Patient Preference and Adherence

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REVIEW

Medication adherence in pediatric transplantation and assessment methods: a systematic review

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Background: Medication adherence is a major concern in public health. It is fully established that immunosuppressive therapy (IT) and concomitant medications affect transplant outcomes in the pediatric population, showing interest in adherence to this therapy. The aim of the present review was to report on medication adherence in pediatric population post-transplantation. This will enable us to know the situation in this particular population.

Methods: A literature search was performed using the MEDLINE database. Studies that were published from January 1999 to January 2016 in English language and which investigated medication adherence in pediatric transplantation were included. The type of organ and the methods used to assess medication adherence were studied.

Results: A total of 281 records were identified, from which 34 studies were selected: 38% (n=13) on kidney transplantation, 32% (n=11) on liver transplantation, and 23% (n=10) on the transplantation of other organs. Medication adherence was found to be lower than 80% in two-thirds of the studies (64%), and varied from 22% to 97%. This wide range was explained in part by the important heterogeneity of assessment methods among studies. The methods used were objective, non-objective, or combined both types. Most studies did not fully describe the data collected: the time since transplantation, the period over which adherence was assessed, the population, the medications, and the threshold discriminating adherence and non-adherence.

Conclusion: The present study found poor medication adherence in the pediatric population post-transplantation. There was a wide range of medication adherence, explained largely by the heterogeneity of assessment methods. Future studies must consider the characteristics of each methodology, but also the threshold defining adherence should be chosen on the basis of clinical outcomes, and describe all data collected to gain precision. To improve adherence in this population, it is essential to identify factors influencing medication (IT and concomitant medications) adherence.

Keywords: medication adherence, patient compliance, child, transplantation

Introduction

Adherence is defined "as the extent to which a person's behavior [...] corresponds with agreed recommendations from a health care provider". Medication adherence averages 50% among adults suffering from chronic diseases, and as poor medication adherence compromises the therapeutic approach it is a major concern in public health.[1]

In adults, immunosuppressive therapy (IT) adherence averages 48% after renal transplantation, which is the most frequent transplant procedure.[2] In adults and pediatric populations, IT is recognized as essential after solid organ transplantation (SOT)[3,4] and hematopoietic stem cell transplantation (HSCT).[5] IT is part of treatment regimen post-transplantation that includes concomitant medications to prevent infection. After SOT in pediatric patients, the risk of biopsy-proven acute rejection is doubled, the risk of

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hospitalization is increased by 60%, and that of organ loss by 80% when patients considered non-adherent to IT.[6] Medication adherence is therefore a major concern in pediatrics. In 2009, Dew et al[49] published a meta-analysis that investigated medical regimen adherence after SOT in a pediatric population; the authors included studies that reported non-adherence to IT and/or clinical appointments. The authors concluded that there was a wide range of IT adherence rates due to the heterogeneity of methodological aspects and analysis of data in published studies. However, there is no recent systematic review that has investigated adherence to both IT and concomitant medications in a pediatric population after both SOT and HSCT. The aim of the present review was therefore to report on medication adherence in pediatric populations after both SOT and HSCT. This will provide an overview in this particular population, and a special focus will be made on the assessment methods used, which can be objective methods such as drug assays, and non-objective methods such as questionnaires.[1,7]

Methods

The MEDLINE database was searched for relevant studies published from January 1, 1999 to January 1, 2016 using the following search strategy: ("patient compliance" [Mesh] OR "medication adherence" [Mesh] OR medication compliance) AND (pediatr* OR child) AND (transplan*). The inclusion criteria were: studies in English language, reporting on pediatric transplant patients (age <21 years at the time of transplantation), measuring medication adherence, and describing the assessment method of medication adherence. Case reports, editorials, letters, and syllabi were excluded. Systematic and non-systematic reviews, as well as meta-analysis were excluded but checked for additional studies.[11,49] The selection was independently reviewed by two of the authors (DH and AJD), and disagreements were resolved by consensus.

The analysis of selected studies consisted of description of organs, mean time since transplantation, population, medications; the methods used to assess medication adherence were also investigated.

Results

The first search strategy found 281 records; 221 were excluded because they did not talk about medication adherence in pediatric transplantation. A further 19 studies were excluded because a measure of medication adherence was not reported, and 7 because results obtained in pediatric subjects were not reported separately from other populations (Figure 1). Thus, 34 studies were included.

Thirteen studies concerned kidney transplantation (Table 1), and 11 liver transplantation (Table 2). Other studies reported IT adherence in heart transplantation (Table 3), HSCT (Table 4), or combined results of

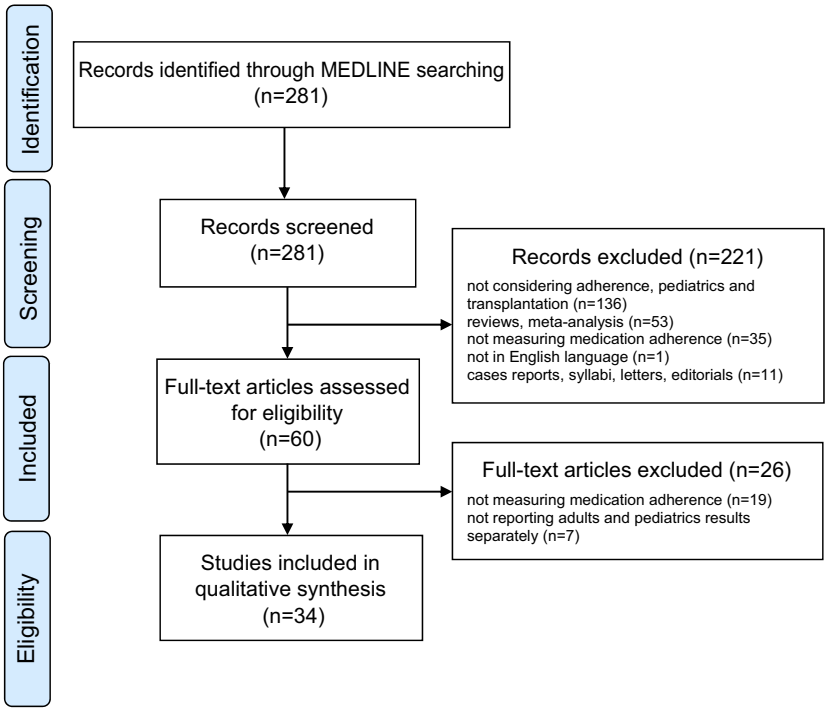

Figure 1 Review inclusion and exclusion flowchart followed PRISMA guidelines.

Table 1 Medication adherence and assessment methods in kidney transplantation

References	Setting & Design	Population	Medications	Mean time since transplantation	Methods	Medication adherence (regarding methods)
Penkower et al, 2003[8]	USA Prospective, longitudinal	n=22 adolescents. Age 13–18 yr (mean 16)	Tac, CsA	4.3 yr	Interview (patient): ≤3 missed doses/month	87%
Shaw et al, 2003[12]	USA Retrospective	n=112. 48 child/64 adolescents Age 9–22 yr (mean 15)	Tac, CsA	5 yr	Drug assay by 2 consecutive levels (Tac<2 ng/mL, CsA<50 ng/mL)	68% Child: 81% Ado: 65%
Gerson et al, 2004[13]	USA Prospective, comparative (methods)	n_1=7 n_2=6. Age 2–21 yr (mean 11)	Tac, CsA	2 m	Gp 1: **Combined**: MEMS over 3 m, drug assay (with gradual physician's opinion) on 6 consecutive levels (Tac 4–12, CsA 100–250 ng/mL) Gp 2: drug assay only	Gp 1: 60% Gp 2: 80%
Feinstein et al, 2005[14]	Israel Retrospective	n=79 adolescents. Age >12 yr	Tac, CsA	ND	**Combined**: drug assay by levels (Tac>2, CsA>20 ng/mL) and/or questionnaire: ≤1 missed, frequency, "drug holiday"	84%
Takemoto et al, 2007[15]	USA Retrospective	n=91 adolescents. Age <18 yr (n=7046 with adults)	Tac, CsA	ND	MPR over 36 m: poor <69%, low 69–81%, medium 81–98%, high >98%. high defining adherent patients	56% (high)
Delucchi et al, 2008[16]	Chili Prospective	n=150 adolescents. Age 10–22 yr (mean 17)	IS	5.8 yr	**Combined**: BM (High creatininemia), drug assay by levels; and if suspected: questionnaire (10 patients/5 caregivers)	90%
Wu et al, 2008[9]	China Retrospective	n=27 adolescents. Age 13–16 yr (mean 14)	Tac, CsA, Aza, pred, MMF	ND (range 5.9–14.7)	Questionnaire	70%
Zelikovsky et al, 2008[17]	USA Prospective	n=56 adolescents. Age 11–18 yr (mean 14)	IS	ND	Questionnaire: MAM >90% or MAM >80%	62% 78%
Chisholm-Burns et al, 2009[18]	USA Retrospective	n=877. Age mean 12 yr	Tac, CsA	ND	MPR over 36 m: Interquartile 4= adherent Interquartile 1–3= non-adherent	92%
Dobbels et al, 2010[19]	Belgium Prospective	n=23 families: 23 adolescents/22 parents Age 11–18 yr (mean 15)	Tac (14), CsA (7), other IS (2)	3.8 yr	**Combined**: Questionnaire BAASIS (patient/caregiver); drug assay by levels (Tac>5, CsA>100 ng/mL); Gradual physician's opinion	22% 26/27% 63% 52%
Ingerski et al, 2011[20]	USA Prospective	n=13 adolescents. Age 14–18 yr (mean 16)	IS	65.5 m	MEMS over 1 m	74%

(*Continued*)

Table 1 (Continued).

References	Setting & Design	Population	Medications	Mean time since transplantation	Methods	Medication adherence (regarding methods)
Pai et al, 2012[21]	USA Prospective	n=48 adolescents. 2 *non-transplanted patients* mean age: 16	Tac, SrL	3.9 *yr*	MEMS over 1 m Questionnaire MAM (patient) Drug assay by SD (Tac): ND Drug assay by <10% level/patient ≤2.5 ng/mL during 2 *yr* (T1=before transition. T2=after transition)	79% 97% (SD: 2.17) 59% n_1=68% n_2=32% (T1=T2)
Akchurin et al, 2014[22]	USA Retrospective	n=46 adolescents. Age ND n_1=25 "child to adult care transition already done" n_2=22 "graft loss before transition"	Tac	ND		

Abbreviations: Ado, adolescents; Aza, Azathioprine; BAASIS, Basel Adherence Assessment Scale for immunosuppressive medication; CsA, cyclosporin; IS, immunosuppressant; m, month; MACS, multidimensional adherence classification system; MAM, medication adherence measure; MEMS, medication event monitoring system; MMF, mycophenolate mofetil; MPR, medication possession ratio; ND, not documented; Pred, prednisone;SrL, sirolimus; Tac, tacrolimus; T1, time 1; T2, time 2; *yr*, year.

different organs in the same study (multi-organ studies) (Table 5).

Among all types of organ, medication adherence ranged from 22%[19]to 97%.[21] Medication adherence was found to be lower than 80% in 22 studies, between 80% and 90% in 5 studies,[8,12,14,23,24] and 90% or greater in 7 studies.[16,18,21,32,34,37,42] Among these 7 studies, 3 focused on kidneys,[16,18,21] 1 on liver,[32] 1 on heart,[34] and 2 were multi-organ.[37,42]

Twenty studies reported the mean time of medication adherence measurement since transplantation, which ranged from 27 days[35] to 9.4 years.[31,33]The majority of these studies (n=12) examined medication adherence 5 years or later after transplantation, and among these medication adherence ranged from 27%[31] to 97% .[37]

The majority of studies (n=23) reported data for adolescents (≥10 years of age) only. Two studies reported data for children, in whom adherence was 30%[41] and 91%.[34] One study stratified according to the patient's age, and concluded that medication adherence was poorer among adolescents (65%) than in children (81%).[12]

All included studies concerned IT. Twenty-two studies measured adherence to cyclosporine (CsA), 26 to tacrolimus (Tac), and 21 to both CsA and Tac. Three studies measured also concomitant medications: antibiotics, antivirals, antihypertensives for instance, without separated IT and concomitant medication adherence measures.[35,41,42] One study compared IT to concomitant medications: IT adherence was poorer (60% vs 80%).[41]

Assessment methodologies

Period over which adherence was assessed

The majority of studies (n=24) reported the period over which adherence was assessed; this ranged from 7 days[17,42] to 36 months.[15,18]The period was related to the method used: medication event monitoring systems (MEMS) generally examined adherence over a 1–6-month period,[13,20,21,35,37]medication possession ratio (MPR) over a 36-month period,[15,18] and medication adherence measure (MAM) questionnaire over a 7-day period.[17,42] Five studies[13,20,21,35,37] examined medication adherence in a 3–6-month period: medication adherence ranged from 60%[13] to 73%.[35] Eight studies[15,18,22,23,29–31,38]examined medication adherence over a 1–2.5-year period: medication adherence ranged from 27%[38]to 92%.[18]

Table 2 Medication adherence and assessment methods in liver transplantation

References	Setting and design	Population	Medications	Mean time since transplantation	Methods	Medication adherence (regarding methods)
Shemesh et al, 2000[23]	USA Retrospective	n=19. Age 9–20 yr (mean 14)	Tac	ND	**Combined**: physician's or nurse's opinion; drug assay by SD during 1 yr	84%
Falkenstein et al, 2004[24]	USA Retrospective	n=234 (n=40 with non-compliance). n=28<10 yr & n=12>10 yr	Tac (11), CsA (29)	ND	**Combined**: BM (Low AST/ALT); drug assay by levels (low levels C0 and C2h)	83%
Rumbo et al, 2004[25]	USA Retrospective	n=14 adolescents. Age 12–17 yr	Aza	ND	Drug assay by SD (metabolite <50 pmol/8X10^8 erythrocytes) during 25m	71%
Shemesh et al, 2004[26]	USA Prospective	n=81. Age 0.5–21 yr (30>8 yr)	Tac, CsA	ND	Drug assay by SD Questionnaire Likert-like scale (patient/care-giver) Nurse's opinion Physician's opinion	(SD 2.48) 70/70% 52% 61%
Berquist et al, 2006[27]	USA Retrospective	n=97 adolescents. Age 12–18 yr (mean 15)	Tac, CsA	ND	RCR	62%
Berquist et al, 2008[28]	USA Retrospective	n=111 adolescents. Age 12–21 yr (mean 15)	Tac, CsA	Non adherent: 12.4 yr Adherent: 9.6 yr	RCR	50%
Fredericks et al, 2008[29]	USA Retrospective	n=38 adolescents. Age 12–18 yr (mean 15)	Tac	7.5 yr	**Combined**: questionnaire MAM (patient) Drug assay by SD (<2) during 1 yr	42%
Stuber et al, 2008[30]	USA Retrospective	n=68 adolescents. Age <21 yr	Tac	ND	Drug assay by SD (≤3) during 2 yr or more	50%
Fredericks et al, 2010[31]	USA Retrospective	n=71 adolescents. Age 11–20 yr (mean 12)	Tac, CsA	9.4 yr	Drug assay by SD (Tac<2, CsA <30) and by levels (<50% out of interval) during 1 yr	30% 27%
Masuda et al, 2010[32]	Japan Retrospective	n=108. Age 9–21 yr (mean 18)	Tac, CsA	8 yr	**Combined**: Interview; and if suspected: Drug assay and BM (AST/ALT)	94%
Bilhartz et al, 2015[33]	USA Retrospective	n=48 adolescents. Age 11–20 yr (mean 16)	Tac	9.4 yr	Drug assay by SD (≤2) during 6 m	67%

Abbreviations: ALT, Alanine Transaminase; AST, Aspartate Transaminase; Aza, Azathioprin; BM, Biological Markers; C0, Residuel concentration; C2h, Concentration 2hours after administration; CsA, Cyclosporin; m, month; ND, Not Documented; RCR, retrospective chart review; SD, Standard Deviation; Tac, Tacrolimus; yr, year.

Table 3 Medication adherence and assessment methods in heart transplantation

References	Setting & Design	Population	Medications	Mean time since transplantation	Methods	Medication adherence (regarding methods)
Oliva et al, 2013[34]	USA Retrospective	n=2030 children. Mean age: 6 yr	IS	ND	RCR	91%

Abbreviations: IS, immunosuppressant; ND, not documented; RCR, retrospective chart review; yr, year.

Table 4 Medication adherence and assessment methods in hematopoietic stem cell transplantation

References	Setting and design	Population	Medications	Mean time since transplant	Methods	Medication adherence (regarding methods)
Mc Grady et al, 2014[35]	USA Prospective	n=6 adolescents. Age 12–18 yr (mean 15) malignant hematology (4), Non-malignant (1), oncology (1)	Tac, CsA, FLC, VRC, ACV, SXT	27 days	MEMS over 3 m	73%

Abbreviations: ACV, aciclovir; CsA, cyclosporin; FLC, fluconazole; m, month; MEMS, medication event monitoring system; ND, not documented; SXT, cotrimoxazole; Tac, Tacrolimus; VRC, voriconazole; yr, year.

Objective methods

Thirty-one studies assessed medication adherence using objective methods: drug assays (n=21), MEMS (n=6), MPR (n=2). A total of 21 studies used drug assays (Table 6) among which 2 did not mention the type of drug assay (level or SD).[32,36] The 21 other studies considered either drug or metabolite levels in plasma, serum, or blood (n=10), and/or the SD that reports drug or metabolite levels over a period of time (n=11). SD studies (performed only for Tac) found medication adherence from 27%[38] to 90%.[41]Studies using levels reported medication adherence that ranged from 27%[31] to 84%.[14] Six other studies used MEMS,[13,20,21,35,37,40] which is a specific medication device recording date and timing of each use, and reported medication adherence ranged from 69%[37] to 79%[21] (Table 6).Two studies used MPR: medication adherence reported was 56%[15] and 92%.[18]

Non-objective methods

Twenty studies assessed medication adherence by non-objective methods: questionnaires or interviews (n=16), the opinion of physicians and/or nurses (n=4), retrospective chart review (RCR; n=3). RCR evaluated the number of patient records documenting medication non-adherence: the medication adherence reported in the 3 studies was 50%,[28] 62%,[27] and 91%.[34] Among the 4 studies using the opinion of physicians and/or nurses,[13,19,23,26] 2 reported medication adherence by this method: 52%[19] and 61%.[26] The medication adherence, reported by the 16 studies using questionnaires and interviews ranged from 26%[19] to 97%.[21] Six studies used the MAM questionnaire,[17,21,38,39,42,43] which is a specific and validated pediatric tool for adherence post-transplantation that evaluates the number of missed or late doses during the previous 7 days. The medication adherence from MAM questionnaire-studies ranged from 65%[17] to 97%.[21] Furthermore, a total of 7 studies reported caregiver or parent's medication adherence. Among these, 3 studies compared patient and caregiver reports and found results that were close: 26% and 27%,[19] 70% and 70%,[26] and 86% and 88%.[39]

Combined methods

Sixteen studies used several assessment methods and a total of 10 studies combined these to calculate medication adherence.[13,14,16,19,23,24,32,38,41,43] With this methodology, medication adherence ranged from 22%[19] to 94%,[32] and 5 studies reported medication adherence greater than 80%.[14,16,23,24,32] Four studies detailed precisely the combination of techniques.[19,38,41,43]

One combination technique defined non-adherence as below a threshold for at least one item used.[19,41] Two studies used a combination of drug assays, nurse/physician's opinion, and basal adherence assessment scale for immunosuppressive medication, a validated questionnaire on a 6-point scale. Medication adherence obtained with this combination technique was 22%[19] and 30%.[41]

Table 5 Medication adherence and assessment methods in multi-organ studies

References	Setting and design	Population	Medications	Mean time since transplantation	Methods	Medication adherence (regarding methods)
Wray et al, 2006[36]	UK Prospective	n=40 adolescents. Age 12–25 yr (mean 18) Heart (33), Heart-lungs (7)	Tac, CsA	8.8 yr	Questionnaire (patient): BMQ and if intentional: drug assay	72% 82%
Maikranz et al, 2007[37]	USA Prospective	n=70. Age 7–18 yr (mean 13) heart (42), kidney (28)	IS	6 yr	MEMS (n=28) over 3 m Questionnaire (caregiver): missed doses past 3 days each month	69% 97%
Simons et al, 2009[38]	USA Prospective	n=68 families: 71 adolescents/78 parents Age 11–21 yr (mean 16) kidney (47), liver (20), heart (14), lung (1)	Tac, CsA, SrL	4.8 yr	**Combined**: MACS: Questionnaire MAM >90%; drug assay (by SD <3 only for Tac) during 1 yr	All organs: 27% kidney: 28% liver: 25% heart: 29%
Simons et a, 2010[39]	USA Prospective	n=66 families: 51 adolescents/62 parents Age 11–20 yr (mean 16) kidney (39), liver (16), heart (10), lungs (1)	Tac, CsA, SrL	ND	Questionnaire MAM >90% (caregiver/patient) Drug assay by levels during 16 m (<1 CsA <150, SrL<5, Tac <4ng/mL or SD<3 only for Tac)	86/88% 57%
Wu et al, 2010[40]	USA Prospective	n=55 adolescents. Mean age: 13 yr liver (32), kidney (23)	Tac, CsA, MMF, SrL, Pred, SXT	6.2 yr	MEMS over 87 days	70%
Claes et al, 2014[41]	Belgium Prospective	n=10 children. Age 2–11 yr (mean 6) kidney (5), liver (5)	Tac (9), CsA (1) comedications	5.5 yr	**Combined**: Questionnaire BAASIS IS/comedications (caregiver) Drug assay (by SD<2 only for Tac) during 6–12 m Nurse's opinion	30% 60/80% 90% 30%
McCormick King et al, 2014[42]	USA Prospective	n=72 adolescents. Age 12–21 yr (mean 18) kidney (37), liver (27), heart (5), heart & kidney (2), kidney & liver (1)	IS and other medications (antihypertensive)	6.7 yr	Questionnaire MAM (patient)	96%
Loiselle et al, 2015[43]	USA Prospective Longitudinal: T1: since transplant. T2: 18 m after T1	N=66 adolescents. Age: ND (mean 15.8) kidney (39), liver (16), heart (10), heart & lung (1)	CsA, Tac, SrL	3.4 yr	**Combined**: MACS: Questionnaire MAM >90% (patient/caregiver); drug assay by levels (<1 level CsA <150, SrL <5, Tac <4 ng/mL or SD<3 only for Tac)	65% 82/73% 33%

Abbreviations: BMQ, Belief about Medication Questionnaire; CsA, cyclosporin; IS, immunosuppressant; MACS, multidimensional adherence classification system; m, month; MAM, medication adherence measure; MEMS, medication event monitoring system; MMF, mycophenolate mofetil; ND, not documented; Pred, prednisone; SrL, sirolimus; SXT, cotrimoxazole; Tac, tacrolimus; T, time; yr, year.

Table 6 Methods used to assess medication adherence

Methods	Nomber of studies concerned	References concerned	Medication adherence prevalence
Drug assays	21	12–14,16,19,21–26,29–33,36,38,39,41,43	27–90%
Questionnaire/interview	16	8,9,14,16,17,19,21,26,32,36–39,41–43	26–97%
Combined	10	13,14,16,19,23,24,32,38,41,43	22–94%
Medication event monitoring system	6	13,20,21,35,37,40	69–79%
Physician or nurse's opinion	4	13,19,23,26	30–61%
Retrospective chart review	3	27,28,34	50–91%

Another combination technique created balance scores of different methods, such as the multidimensional adherence classification system (MACS),[38,43] which is a validated tool combining the MAM questionnaire and drug assay. Two studies used this technique: medication adherence was 27%[38] and 65%.[43]

Discussion

To the best of our knowledge, this is the first time a systematic review has focused on medication adherence in a pediatric population after both SOT and HSCT. A total of 34 studies investigated medication adherence after transplantation over the last 16 years in pediatric populations, which is low considering the number of studies in other chronic diseases.[44] Irrespective of the transplanted organ, medication adherence ranged widely among studies. It remained poor with two-thirds studies (64%) describing medication adherence lower than 80%, highlighting the importance of considering medication adherence in the pediatric population post-transplantation.

Data for HSCT, a relatively frequent procedure, is reported only in one study,[35] whereas two studies reported data for heart-lung transplantation which is a rare procedure.[34,36] This may be related to the short period required of IT after HSCT, as compared to the indefinite period required after SOT. Nevertheless, IT is essential for good prognosis after HSCT,[5] and it is therefore of great interest to evaluate medication adherence after such transplantations.

All studies in this review investigated adherence to IT, underlining the importance of this concern in the post-transplantation period. Despite the need for an effective prevention of infections after transplantation, for instance, only 3 studies reported adherence to concomitant medications such as antibiotics.[35,41,42] In adults, Russel et al have considered that adherence to a medication – measured by MEMS – allowed the extrapolation of results to the comedications.[45] However in pediatrics, it is more appropriate to evaluate medication adherence for individual drugs[41,46] as aspects such as medication flavor or form (syrup or pill) could cause different behaviors in children.[7] It would be interesting that the 3 studies found in this review did compare IT adherence to concomitant medication adherence.

Most studies reported data for adolescents, which reflects a concern regarding medication adherence in this specific population after SOT and HSCT. Only one study compared data for children and adolescents, which is regrettable. This study revealed that medication adherence in children (81%) is higher than in adolescents (65%).[12] The adolescence period of life is known to decrease medication adherence by several reasons;[7] for instance, Dobbels et al enunciate the transition to adulthood health care system as an important factor of non-adherence during adolescence.[10] This is confirmed by a study included in this present review which found that IT adherence after transition (32%) is lower than before (68%).[32] In addition, adolescence is a time when difficulties in the parent–patient relationship are important.[7] Regarding it, the unfrequent comparison of adolescent and caregiver reports on medication adherence (3 studies in this review using subjective methods) would be interested to consider more.

An important aspect to consider when interpreting data is the measurement method employed. At the time of writing no "gold standard" method exists,[1,7] which explains the heterogeneity of those used in this review. Surprisingly, 16 studies used only 1 method whereas it is known that no single method is optimal.[1,7] For example,

Table 7 Assessment methods and definition of medication adherence or non-adherence by authors

References	Definition of medication adherence (MA) or medication nonadherence (MNA) by authors	MA or MNA	Methods	*A priori* threshold of MA
Penkower et al, 2003[8]	How often patients missed taking prescribed medication (seven options ranging from missing medication severy day to never missing medications). Nonadherent if they missed taking medications at least 3 times in a month.	MNA	Interview (patient): ≤3 missed doses/month	Not documented
Shaw et al, 2003[12]	Non-adherence if the patient had consistently and significantly low serum IS levels (Tac<2 ng/mL, CsA<50 ng/mL) on a minimum of 2 consecutive levels without maintenance dose change, unaccompanied by an explanation of lack of absorption	MNA	Drug assay by 2 consecutive levels (Tac<2 ng/mL, CsA<50 ng/mL)	Not documented
Gerson et al, 2004[13]	*"Medication adherence reported as a percentage and calculated by dividing the number of recorded presumptive medication doses by the number of prescribed dose and then multiplying the quotient by 100. Also, 2 nephrologists classify as 'probably adherent' to 'possibly non-adherent' regarding the target range"*	MA	Gp 1: **Combined**: MEMS over 3m, drug assay (with gradual physician's opinion) on 6 consecutive levels (Tac 4–12, CsA 100–250 ng/mL) Gp 2: drug assay only	Not documented
Feinstein et al, 2005[14]	*"Noncompliant behavior was defined as discontinuation of 1 or more IS medications, deviation from prescribed dose or frequency, and/or 'drug holidays'. Patients seld reports and/or levels served as indicator (Tac<2, CsA<20 ng/mL) of non-compliance"*	MNA	**Combined**: drug assay by levels (Tac>2, CsA>20 ng/mL) and/or questionnaire: ≤1 missed, frequency, "drug holiday"	Not documented
Takemoto et al, 2007[15]	We modeled compliance as a time-varying variable by splitting patients into quartiles based on overall 1–3 MPR values: poor compliance when MPR fell below 69%, low for MPR between 69 and 81%, medium for MPR 81 and 98% and high when the MPR exceeded 98%	MA	MPR over 36 m: poor <69%, low 69–81%, medium 81–98%, high >98%	>98%
Delucchi et al, 2008[16]	*Not documented*	MNA	**Combined**: BM (High creatininemia), drug assay by levels; and if suspected: questionnaire (10 patients/5 caregivers)	Not documented
Wu et al, 2008[9]	*Not documented*	MNA	Questionnaire	Not documented
Zelikovsky et al, 2008[17]	*"Classifying patient as adherent or not adherent is also possible by selecting cut off with regard to percent adherence"*	MA	Questionnaire: MAM >90% or MAM >80%	>90% >80%
Chisholm-Burns et al, 2009[18]	We also calculated MPR quartiles and used these date to classify pediatric renal transplant recipient into binary (adherent and nonadherent) groups. MPR Quartile 4 (the highest quartile) was classified as the adherent groupe and MPR quartile 1 to 3 were collapsed and classified as the nonadherent group.	MA	MPR over 36 m: Interquartile 4= adherent Interquartile 1–3= non-adherent	>75%
Dobbels et al, 2010[19]	Non-adherence is defined as any self-reported non-adherence (response score 1–5) on any of the four items [BAASIS questionnaire]. the four trough blood levels for cyclosporine or tacrolimus preceding the data collection were retrieved from the medical charts, with a tacrolimus trough level below 5 ng/mL, and a cyclosporine level below 100 ng/mL on at least one measurement being indicative for non-adherence	MNA	**Combined**: Questionnaire BAASIS (patient/caregiver); drug assay by levels (Tac>5, CsA>100 ng/mL); Gradual physician's opinion	Not documented

(*Continued*)

Table 7 (Continued).

References	Definition of medication adherence (MA) or medication nonadherence (MNA) by authors	MA or MNA	Methods	*A priori* threshold of MA
Ingerski et al, 2011[20]	*"Adherence was defined as the number of doses of oral medication taken divided by the number prescribed across the 1-month period"*	MA	MEMS over 1 m	Not documented
Pai et al, 2012[21]	[MEMS] Adherence was defined as the number of times that doses of oral medication were taken out of the number of doses prescribed within a 30-day period. [MAM] Adherence was defined as the number of times that doses of oral medication were taken out of those prescribed during the designated sevenday time period. [drug assay] A larger SDTACRO or SDSIRO is considered *indicative of poorer adherence.*	MNA	MEMS over 1 m Questionnaire MAM (patient) Drug assay by SD (Tac): ND	Not documented
Akchurin et al, 2014[22]	*"Based on the percent of low tacrolimus levels, we categorized patients as nonadherent if they had more than 10% of low levels during the period of observation and as adherent otherwise"*	MNA	Drug assay by <10% level/patient ≤2.5 ng/mL during 2 yr (T1=before transition. T2=after transition)	>90%
Shemesh et al, 2000[23]	*"higher SD, and therefore, increased variability between individual levels overtime, is a fairly specific but not a sensitive measure of nonadherence in our population"*	MNA	**Combined**: physician's or nurse's opinion; drug assay by SD during 1 yr	Not documented
Falkenstein et al, 2004[24]	*Not documented*	MNA	**Combined**: BM (Low AST/ALT); drug assay by levels (low levels C0 and C2h)	Not documented
Rumbo et al, 2004[25]	*Not documented*	MNA	Drug assay by SD (metabolite <50 pmol/8X10^8 erythrocytes) during 25 m	Not documented
Shemesh et al, 2004[26]	*"[SD] higher SD means a higher degree of difference between individual levels, which suggests less consistent medication taking and, therefore, less adherence [questionnaire] scale, 1 "I always take my medications as prescribed," 2 "I mostly take my medications as prescribed," 3 "I sometimes take my medications as prescribed," and 4 "I rarely take my medications as prescribed".*	MA	Drug assay by SD Questionnaire Likert-like scale (patient/caregiver) Nurse's opinion Physician's opinion	Not documented
Berquist et al, 2006[27]	*"non-adherence was defined prior to data collection as any documented report by a patient, parent or health care provider of non-adherence to immunosuppressive medication taking by the patient that was formally recorded in the patient's legal medical record. Any patient with at least one episode of chart-documented non-adherence to taking the immunosuppressive medication after 1 yr post-transplantation was considered to be non-adherent in our study."*	MNA	RCR	Not documented

(*Continued*)

Table 7 (Continued).

References	Definition of medication adherence (MA) or medication nonadherence (MNA) by authors	MA or MNA	Methods	*A priori* threshold of MA
Berquist et al, 2008[28]	*"non-adherence was defined as patient admission of not having taken the immunosuppressive(s) medication or not having attended an annual clinic visit in 2005. Any patient with at least one episode of not taking the immunosuppressive medication as prescribed by the healthcare provider after the six month post-transplantation visit was considered to be non-adherent. This definition included patients who changed the dose, those who took fewer doses, and a subgroup who made the independent decision to stop their immunosuppression completely without the healthcare provider's knowledge"*	MNA	RCR	Not documented
Fredericks et al, 2008[29]	*"Adherence was defined as s.d. <2"*	MA	Drug assay by SD (<2) during 1 yr	SD <2 for Tac
Stuber et al, 2008[30]	*Not documented*	MNA	Drug assay by SD (≤3) during 2 yr or more	Not documented
Fredericks et al, 2010[31]	*"adherence was defined as a tacrolimus SD <2 and cyclosporine SD<30, and/or <50% of immunosuppressant blood values out of the target range »*	MA	Drug assay by SD (Tac<2, CsA <30) and by levels (<50% out of interval) during 1 yr	SD <2 for Tac
Masuda et al, 2010[32]	*"Noncompliance was defined as not taking the immunosuppressant medication"*	NMA	**Combined**: Interview; and if suspected: Drug assay and BM (AST/ALT)	Not documented
Bilhartz et al, 2015[33]	*Not documented*	MA	Drug assay by SD (≤2) during 6 m	SD <2 for Tac
Oliva et al, 2013[34]	*"Patient was defined to be NA when first reported to be so, irrespective of subsequent reports of adherence."*	MNA	RCR	Not documented
Mc Grady et al, 2014[35]	*"Daily adherence was calculated by dividing the number of pill bottle openings per day by the number of prescribed doses for that day. Weekly and monthly adherence values were calculated by computing the mean of daily adherence values across the specified time frame"*	MA	MEMS over 3 m	Not documented
Wray et al, 2006[36]	Those patients who reported forgeting to take their medications regularly in response to a specifiqc quetsion on the BMQ questionnaire were considered to be unintentionnaly non-adherent. The second response was non-adherence which had been specified in the medical notes and which had been documented by the consultatn cardiologist as intentional non-adherence	MNA	Questionnaire (patient): BMQ and if intentional: drug assay	Not documented

(*Continued*)

Table 7 (Continued).

References	Definition of medication adherence (MA) or medication nonadherence (MNA) by authors	MA or MNA	Methods	*A priori* threshold of MA
Maikranz et al, 2007[37]	Adherence as assessed by MEMS was calculated as the number of recorded doses divided by the number of prescribed doses over the 3-month study period. Self-reported adherence was calculated as the percent of prescribed dose that were successfully admiinistrered for each medication.	MA	MEMS (n=28) over 3 m Questionnaire (caregiver): missed doses past 3 days each month	Not documented
Simons et al, 2009[38]	*"MACS places each patient into one of four categories based on parent/self report and immunosuppressant levels [Table 3]"*	MNA	**Combined**: MACS: Questionnaire MAM >90%; drug assay (by SD <3 only for Tac) during 1 yr	>90% SD<3 for Tac
Simons et a, 2010[39]	*"The final dichotomous categorization of drug levels, as "adherent" or "non-adherent"was determined by the presence of one or more out-of-range blood levels of tacrolimus with SD>3"*	MNA	Questionnaire MAM >90% (caregiver/patient) Drug assay by levels during 16 m (<1 CsA <150, SrL<5, Tac <4 ng/mL or SD<3 only for Tac)	>90% SD<3 for Tac
Wu et al, 2010[40]	*"For each day of monitoring, a continuous measure of medication adherence was calculated by dividing the number of bottle openings by the number of prescibed dosage per day"*	MA	MEMS over 87 days	Not documented
Claes et al, 2014[41]	When combining those 3 elements, the patient was considered nonadherent if he or she scored non-adherent in at least 1 of 3 of the following measures. (..) A score of 1 or higher on at least 1 of 4 questions [BAASIS] is considered as non-adherence. (..) A standard deviation of at least 2 is indicative of non-adherence (..). Average or bad [adherence; as scored by nurses] were therefore considered as medication nonadherent	MNA	**Combined**: Questionnaire BAASIS IS/comedications (caregiver) Drug assay (by SD<2 only for Tac) during 6–12 m Nurse's opinion	SD<2 for Tac
McCormick King et al, 2014[42]	*"Percentage of missed and late doses were calculated by dividing the total number of missed or late doses by the total number of prescribed doses in the previous 7 days"*		Questionnaire MAM (patient)	Not documented
Loiselle et al, 2015[43]	*"Participants who missed or were late in taking 10% or more of their prescribed doses in the past week were classified as " non-adherent" (..)* *Based on these empirically derived out-of-target ranges, participants were coded as "non-adherent" if they had at least one serum levels that fell out of the target ranges (high or low levels for CsA, SrL, Tac, or >3 s.d. for Tac) and adherent if all levels were within the specified ranges."*	MNA	**Combined**: MACS: Questionnaire MAM >90% (patient/caregiver); drug assay by levels (<1 level CsA <150, SrL <5, Tac <4 ng/mL or SD<3 only for Tac)	>90% SD<3 for Tac

Abbreviations: Ado, adolescents; ALT, alanine transaminase; AST, aspartate transaminase; Aza, azathioprine; BAASIS, Basel Adherence Assessment Scale for immunosuppressive medication; BM, biological markers; C0, Residual concentration; C2h, concentration 2 hrs after administration; CsA, cyclosporin; IS, immunosuppressant; m, month; MACS, multidimensional adherence classification system; MAM, medication adherence measure; MEMS, medication event monitoring system; MMF, mycophenolate mofetil; MPR, medication possession ratio; ND, not documented; Pred, prednisone; RCR, retrospective chart review; SrL, sirolimus; Tac, tacrolimus; T1, time 1; T2, time 2; yr, year.

drug assays will not detect patients who take their medications only before clinical visits. Conversely, MEMS is a longitudinal method taking into account "drug holidays" (when a patient discontinues medication of his/her own accord). Nevertheless, patients cannot be blinded to MEMS; it interferes with daily life and causes anxiety.[45] In pediatric patients, all these methods have additional drawbacks. For instance, MEMS-based studies may be too difficult to be feasible in pediatric patients who are unable to take pills,[20,21,35,40] and drug assay methods are invasive so this may be a limiting factor in pediatric patients.[46] Yet, 23 of the 34 studies used this method, which could indicate that this is not a drawback too hard to surpass. In this review, only 10 studies (32%) used combined methods – 4 were published before 2005 and 6 after 2008 – suggesting that this is yet to become the preferred method. Among these studies, only a minority described precisely the combination method although this is essential to interpret data as the different combination techniques have different aims. One of the combination techniques has a high sensitivity: it underestimates medication adherence but misses less frequently non-adherent patients.[19,41] Whereas the other combination technique used a well-balanced score (MACS),[38,43] which allows categorization of patients according to their adherence.[47]

An additional difficulty for the interpretation of data in the present review is the definition of medication adherence which differed between each selected study, as synthetized in the Supplementary material (Table 7). It is interesting to note that many studies did not define a threshold discriminating medication adherence and non-adherence, and when they did so this was rarely based on clinical outcomes. Generally, 80% of taken medication is the arbitrary threshold discriminating medication adherence and non-adherence.[1] To be relevant this threshold should be correlated to clinical outcomes, which was a posteriori investigated in 2 studies included herein; these found a close relationship between IT adherence and graft survival (p=0.017;[18] p=0.02[48]) and also mortality (p=0.009).[48] Also, Stuber et al[30] constructed ROC curve to try answering about the appropriate SD cut-off for Tac.

Limitations

This review included studies from the MEDLINE database only. Given the topic of this review, studies are essentially published in PubMed and research on other database is unlikely to have added additional relevant articles. An additional point is that this review is not a meta-analysis. Dew Ma et al published a meta-analysis in 2009 focusing on medication adherence after pediatric SOT only.[49] The authors recognized that there was a lack of studies in certain transplantation types (lung, intestine) and noted the heterogeneity in published articles concerning methodological aspects and the analysis of data. This still seems to be the case 10 years later.

Conclusion

This review revealed the poor medication adherence in the pediatric population post-transplantation, and underlined also the wide range of medication adherence reported in the literature. The heterogeneity of assessment methods explained at least in part this wide range found. Future studies must weigh the advantages and disadvantages of each methodology and describe all data collected to gain precision. It is also essential that the threshold discriminating adherence and non-adherence must be chosen on the basis of clinical outcomes. Beyond the observation of poor medication adherence, there is an obvious need to improve this situation. For that it is essential to identify factors of medication non-adherence to propose adapted interventions and so try to improve medication adherence in adolescents and children after SOT and HSCT.

Disclosure

The authors report no conflicts of interest in this work.

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