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Factors that positively or negatively influence medication adherence in pediatric liver and kidney transplantation patients

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ABSTRACT

Achtergrond. Patiënten nemen na orgaantransplantatie chronisch immunosuppressiva en co-medicatie om greffeverlies en orgaanrejectie te voorkomen. Dit regime correct volgen blijkt echter vaak moeilijk voor patiënten, ook voor jonge kinderen en hun ouders. Ongeveer 30% van pediatrische patiënten na lever- of niertransplantatie blijkt therapieontrouw met de voorgeschreven medicatie. Factoren kunnen medicatietrouw negatief (barriers) of positief beïnvloeden (facilitatoren). In de literatuur worden steekproeven met een gemengde leeftijd gehanteerd, waardoor prevalentiecijfers en barriers specifiek voor jonge kinderen (i.e. < 12 jaar) onduidelijk zijn. Over facilitatoren bestaat tot heden geen evidentie.

Doelstellingen. Bij kinderen t.e.m. 11 jaar wordt enerzijds de prevalentie van medicatieontrouw van zowel immunosuppressiva als co-medicatie nagegaan. Anderzijds worden barriers en facilitatoren geïdentificeerd en gerelateerd aan socio-demografische en klinische variabelen.

Design. Een consecutive mixed methods design (QUALquan) wordt gehanteerd.

Methode. Tien kinderen voldeden aan de inclusiecriteria. Prevalentie van medicatieontrouw werd onderzocht a.d.h.v. een driedelige methode: het BAASIS© interview, standaarddeviaties van tacrolimus bloedniveaus en een beoordeling door een ANP. Barriers en facilitatoren werden bevraagd in een diepte-interview met hun ouders. Aanvullend werd de IMAB-vragenlijst afgenomen waarin barriers eveneens werden bevraagd. De interviews werden verbatim uitgeschreven en geanalyseerd via inhoudsanalyse. Kwantitatieve data werd verwerkt met behulp van SPSS.

Resultaten. Zeventig procent van de deelnemers bleek ontrouw aan immunosuppressiva; 20% bleek ontrouw aan co-medicatie. De meest frequente barriers zijn vergeetachtigheid van de ouders (70%), het kind geeft de medicatie over (70%), slechte smaak van de medicatie (60%), en breken van de routine (50%). Bij immunosuppressiva komt het overgeven meer naar voor (30%); bij co-medicatie wordt de slechte smaak het vaakst genoemd (50%). De meest frequente facilitatoren zijn medicatie overal meenemen (100%), minder medicaties/regimeveranderingen (80%), en medicatie-inname vergemakkelijken (70%). Ouders die hun kinderen als medicatieontrouw inschatten, die oudere kinderen hadden, en kinderen hadden die op latere leeftijd getransplanteerd werden, rapporteerden meer barriers. Dezelfde patronen werden vastgesteld voor barriers, waarbij ook ouders van jongens meer facilitatoren rapporteerden.

Conclusie. Deze studie biedt innovatieve informatie betreffende medicatieontrouw bij pediatrische orgaantransplantatie, eerst en vooral omdat het gaat om een strikt pediatrische steekproef. Verder wordt onderscheid gemaakt tussen medicatieontrouw aan immunosuppressiva en co-medicatie. Naast barriers worden facilitatoren uitgediept, die in voorgaande studies onterecht over het hoofd werden gezien. Deze studie biedt nieuwe evidentie die van groot nut kan blijken bij de begeleiding van deze patiëntengroep en is een aanzet tot meer diepgaand onderzoek en het ontwikkelen van medicatietrouw verhogende interventies.

Kernwoorden: pediatric – transplantation – kidney – liver – medication adherence – barriers – facilitators

Factors that positively or negatively influence medication adherence in pediatric liver and kidney transplantation patients

(Post transplant medication nonadherence)

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INTRODUCTION

Organ transplantation substantially improves survival and life quality of young patients with terminal organ failure. Since the start of our pediatric program, a total of 37 liver transplantations in 36 children and 151 kidney transplantations in 135 children were performed with a one year patient survival of 92% and 97% respectively (1). Yet, organ transplantation doesn't offer a complete 'cure': the patient remains in a state of chronic illness after transplantation, which needs to be monitored systematically for the rest of his or her life (2). The patient needs to take immunosuppressants post-transplant to avoid organ rejection, graft loss and hence premature mortality (2-5). Systematic reviews show that about 15% of graft losses and one third of late acute rejections are due to nonadherence to the immunosuppressive regimen (6-8,10). Fine et al. (2009) defines medication adherence as: "Deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect (7)." Despite the negative outcomes related to the incorrect management of the medical regimen, pediatric patients often still don't take their medication as they should and it seems that medication nonadherence does occur relatively often (2-10).

About 17 to 30% of pediatric liver and 30 to 32% pediatric kidney transplant recipients are nonadherent to their immunosuppressive regimen (4-10). Most studies however, focus exclusively on adolescent patients as they are the most vulnerable for nonadherence. Others include patients with a large age span, ranging from 0 to 25 years old (3,5-11). The prevalence of nonadherence to the immunosuppressive regimen in early childhood or non-adolescent pediatric transplant patients (i.e. < 11 years of age) is currently unclear (4,6-10). Studies also tend to focus exclusively on immunosuppressants, while most patients also take other medication. De Bleser and colleagues (no date) recently found that nonadherence to co-medications (21.4%) in adult patients is much higher than to the immunosuppressive medications (15.2%). The degree of nonadherence to co-medication however, has not been studied by others (12). In younger patients, parents are typically responsible for the medication management although shared responsibility is possible when children are growing up (3). It would be interesting to know how well parents and young children are able to follow the medication regimen, and whether these factors differ depending on type of medication.

Theoretical models explaining behavior show that barriers are one of the strongest predictors of nonadherent behavior and hence represent a potential pathway to develop strategies to overcome barriers and improve adherence (13,14). Very few papers however, reported on barriers towards medication taking in young pediatric patients, with forgetfulness of both children and parents, angry feelings towards his or her parents, the conviction that he or she doesn't need the medication, presence of side effects, the medication's bad taste, and interference of medication taking with school or social activities. To our knowledge, none of the publications explored facilitators although these might yield additional relevant insights if one plans to develop adherence-enhancing interventions (10).

The systematic review of Dobbels et al. (no date) states the following definition of barriers: Barriers are defined as personal or environmental constraints that are perceived by the patient as undesirable, practical blocks to health-promoting behavior and that prevent patients from acting on their intentions. Accidental or 'unintentional' barriers refer to factors that are beyond a person's control, such as forgetfulness or inability to pay for medication. Purposeful or 'intentional' barriers are circumstances that result in a patient's deliberate decision not to follow the treatment

recommendations, like not taking your medication because you notice no effect, or because you experience side effects (14)." Glasgow (no date) defines a facilitator as "a support for a given behavior" (15). Literature shows that studies focus solely on barriers and fail to investigate facilitators which can cause a positive effect (10). A lot of patients indeed succeed in being adherent to their medication, but it seems that this source of information is seldom utilized. The Positive Deviance initiative also emphasizes this matter: "Positive Deviance is an approach to behavioral and social change based on the observation that in any community, there are people whose uncommon but successful behaviors or strategies enable them to find better solutions to a problem than their peers, despite facing similar challenges and having no extra resources or knowledge than their peers. These individuals are referred to as positive deviants (16)." This approach has been implemented internationally with great success in various sectors. In the healthcare sector, it has for example been used to decrease the number of hospital-acquired infections. The Center for Disease Control and Prevention found a decrease in numbers of 30-73% when evaluating pilot programs in the U.S. (16). Therefore we must consider not only negative, but also positive aspects of medication adherence so we can use this extremely valuable information to further elaborate and improve guidance of transplantation patients and their parents.

The research questions of this mixed methods study are therefore the following:

1. What is the prevalence of medication nonadherence to immunosuppressants and co-medication amongst non adolescent pediatric liver and kidney transplant patients?
2. Which factors positively or negatively influence regular medication taking?

METHODS

Design

We used a consecutive mixed methods (QUALquan) design, combining qualitative research methodology with quantitative cross-sectional questioning. More specifically, insights on barriers and facilitators were gathered through semi-structured depth interviews with the parents followed by a quantitative evaluation of the degree of adherence to the immunosuppressive regimen, as well as the prevalence of pre-identified barriers using standardized questionnaires.
We decided to collect the data through the parents, as they are in general responsible for medication administration.

Research setting and sample

The research took place at the department for pediatric transplantation of the University Hospitals of Leuven, Belgium. Given the small number of eligible participants purposive sampling was not possible, hence we decided to enroll all participants that fulfilled the following criteria:

- Parents of children ≤ 11 years;
- the child underwent a liver or a kidney transplantation;
- the transplantation occurred at least 6 months ago; and

- at least one of both parents was Dutch speaking. Parents who, according to the treating physician or the ANP, do not have the mental capacity to complete an interview or parents who did not have a scheduled hospital appointment for their children within the study period were excluded from this study.

Data collection procedure

A list of persons who qualified for participation was obtained through the ANP. Parents were informed about the research by their treating physician and the ANP during a scheduled consultation from November 2011 to May 2012. Subsequently, parents were contacted by phone by the researcher (Claes), who offered information about the purpose and content of the study in a standardized way and asked for oral informed consent. If parents agreed to participate, an appointment for an interview was scheduled. One or both parents could be present during the interview. The interview was preferably conducted with the person being responsible for medication administration. This appointment could take place in the hospital or at another convenient location of the parent's choice. At the start of the interview, the information was repeated, potential questions were answered and the written informed consent was signed. The selected parents were assured of complete data anonymity. The interviews were conducted in a quiet room and audio taped. The child was allowed to be present. The total procedure, i.e. conducting the interview with the parents followed by filling out the BAASIS© Interview and the IMAB, would take approximately 1.5 hours.

Variables and measurement

Socio-demographical and clinical variables

The following socio-demographical and clinical variables were collected through an interview or chart review:

- Child: gender, age, age at time of transplantation, pre-transplantation diagnosis, type of transplantation (liver, kidney; living versus cadaveric donor transplantation).
- Parents: gender, age, marital status (married or living together, divorced or other), employment status (one out of both parents work or both parents work).
- Who takes responsibility for the medication administration of the child (both parents equally, one parent takes on more responsibility, potential child responsibility)

Qualitative research section

Parents were asked to complete a socio-demographic data form before starting the semi-structured interview, following an interview guide developed prior to the start of the interview (appendix 1 and 2). Topics addressed refer to regimen complexity, medication management in view of preparation and time of administration, and factors positively or negatively influencing medication intake (barriers and facilitators). Probe questions were used to prevent long silences and expand responses. Before starting the interviews, a pilot interview was carried out with parents of a 12 year old child (i.e. who does not meet the inclusion criteria in order not to reduce our limited sample size any further) to evaluate the appropriateness of the interview guide and the interview style. No adaptations were needed.

Quantitative research section

Prevalence of medication nonadherence

According to literature, it's recommended to combine multiple methods to measure medical adherence. In this research we used self-report from parents, blood levels and estimation by the ANP (11). When combining these three elements, the patient was considered nonadherent if he or she scored nonadherent in at least one of three measures.

The BAASIS© Interview (the Basel Assessment of Adherence to Immunosuppressive Medications Scale) is a self-report interview and consists of four questions. Taking nonadherence (defined as the number of missed dosages in the last four weeks), dosage nonadherence (whether the patient decreased the prescript dosage on his or her own initiative), timing nonadherence (how many times does the patient take his or her tablet two hours earlier or later than the prescript timing), and drug holidays (whether the patient missed two or more consecutive doses). The parents needed to respond on a 6-point scale that ranges from zero (never) to five (every day). A score of one or higher on at least one of the four questions is considered as nonadherence. The interview was completed twice, i.e. once to evaluate adherence to the immunosuppressive regimen and once to evaluate adherence to co-medication, as patients typically take other drugs to prevent or treat co-morbidities. The systematic review of Dobbels et al. (2010) states that the BAASIS© Interview is a reliable and valid instrument (17,18).

Immunosuppressant *blood levels* were looked up from the patients' medical files, more particularly, the last five blood levels of tacrolimus. From these, standard deviations (SD) were calculated. Two cut-off points can be considered when evaluating these standard deviations. The first, a standard deviation of 2, is a subclinical cut-off point where associations with variables can arise. The second, a standard deviation of 3.5, is a clinical cut-off point where a real risk of organ rejection occurs. A standard deviation of less than 2 or less than 3.5 respectively, means the patient is medication adherent. One patient takes Neoral® and therefore doesn't have a calculated standard deviation. Cyclosporine blood levels aren't used since they aren't that dependable (19).

Thirdly, the patient's medication adherence was also scored by the *ANP* of the department for pediatric transplantation at the University Hospitals of Leuven. More specifically, she scored the patients' medication adherence as excellent, average or bad. Average and bad were considered as medication nonadherent. She scored the child's medication adherence independently, not being aware of information from the interviews or standardized instruments . This was done intentionally to avoid an observer bias.

Barriers for medication intake

The IMAB (Immunosuppressive Medication Adherence Barriers scale) is a checklist for barriers and consists of 28 personal of environment related limitations that may interfere with the medication intake. Some questioned barriers are for example forgetting to take the medication, not having refills on time, difficulty swallowing the medication, … These 28 items are scored on a 4-point Likert scale. This scale has been developed for adult populations. The list of barriers was presented to the parents, in order to unravel additional barriers that were not mentioned during the interview. The total number of barriers can be calculated from this scale, yet, the IMAB was rather used to complement the information

collected from the interviews. The IMAB hasn't been validated yet, but consists of barriers which are mentioned in existing instruments, but these instruments prove to be insufficient (20).

Data analysis

Qualitative research section

The audio taped interviews were transcribed verbatim, followed by content analysis (21,22). Transcripts were read repetitively, indicating meaningful text fragments referring to barriers and facilitators related to medication that parents experience in the present. Past barriers and facilitators weren't questioned in order to confine the research so we would be able to investigate the predetermined research questions more in depth. The identified barriers and facilitators were listed, then categorized in meaningful categories and quantified. Although this wasn't an initial goal, when analyzing data it became apparent that while parents often identify barriers and facilitators concerning medication in general, they also sometimes allocate some barriers or facilitators specifically to a type of medication. Therefore, a distinction between immunosuppressants and co-medication was made. Potential influencing factors were taken into consideration, such as one or two parent family, the parents' employment status, and the child's age (0-6, 7-11 years).

It's necessary to take some elements into account so authenticity can be pursued as much as possible. First of all, the researchers set their preconceptions aside in order to be objective (bracketing). Secondly, the subject was viewed from multiple angles to maintain result validity (triangulation). Thirdly, the results were described sufficiently to foster generalizability (thick description). Finally, it's important to adjust the sample until no new findings emerge out of the results and enough information has therefore been obtained from the interviews (saturation). Process steps and all documentation were systematically collected and submitted to the promoters and the work supervisor (audit trail). They were able to audit the research process and preserve the student researcher's objectivity/neutrality (21,22).

Quantitative research section

Research data gained through the IMAB and the BAASIS© Interview, as well as socio-demographical and clinical data, was analyzed with the aid of SPSS. Descriptive statistics techniques were used as follows:

- Percentage of medication nonadherence (% intake nonadherence, % dosage nonadherence, % time nonadherence and % drug holidays).
- Standard deviations of tacrolimus blood levels (= Prograft®), based on the last five blood levels (adherent, non adherent).

Data synthesis

After the subsequent collection of qualitative data and quantitative data, both were analyzed separately. Then they were compared to each other and combined. Research question one, relating to the prevalence of medication adherence, was answered through quantitative research. Research question two (barrier and facilitators) were mainly answered through qualitative research. Quantitative data was used to complement qualitative data: did other barriers which hadn't been

identified by parents in the interviews come forward in the IMAB, were barriers and facilitators different in adherent versus non adherent children, etc. Qualitative data are therefore the main focus. Combining these two types of data offered more depth in the results. The final conclusions concerning the predetermined research questions were drawn from these results.

RESULTS

Demographic and clinical characteristics of the participants

Parents of eighteen children were invited to participate. Seven parents declined to take part in this research, mostly because participation in the study was perceived as too time consuming. One parent who could not to take part due to practical issues, was parent to two of the invited patients. One additional family could not be reached which was expected as they don't attend clinic visits either. The final sample therefore consisted of ten children up to eleven years, consisting of parents of five boys and five girls. Table 1 presents the socio-demographic and clinical data of children and parents. The children's median age was 7 years, ranging from 2 to 11 years. Five transplantations were kidney transplantations, the other five were liver transplantations. The median age at the time of transplantation was 1 year with a range from 4 months to 5 years. One child was retransplanted (one at the age of four and one at the age of nine). Eight parents are either married or living together; two are divorced. Five children do not have brothers or sisters. All children received a transplantation due to a congenital disease. Parents were interviewed at a median age of 63 months post-transplant.

Patients receive either Neoral® (10%) or Prograft® (90%) as basic immunosuppressive therapy. Some children take Cellcept® (20%), Prednisolone® (40%), and/or Imuran® (10%) complementary. All children take co-medication: a range of 24 different co-medications are used in the children's medication regime (f.e. vitamin D, growth hormone, natrium bicarbonate, …) with a median of 3.5 co-medications (range 1-10). The median total number of medications that a child has to take is 5.5, with a range from two to eleven. Immunosuppressants have to be taken twice a day, with twelve hours in between administrations. All parents approximately give them at eight o'clock AM and PM, because these are on the one hand the medication times that were used in the hospital and because they fit within their daily routine on the other hand (see Table 1).

Fifty percent of the parents share the responsibility equally amongst each other. In 50% one parent takes on most of the responsibility (40% mother, 10% father), either because one is a stay-at-home parent or has a medical background. In one case, the mother is solely responsible because she's divorced and the father doesn't want to take part in the medication regimen. Fifty percent of children take up some of the responsibility (mostly trying to remember to take the medication themselves), while 50% can't because they're too young. The median age of children who share responsibility for medication management, is 10 years with a range from six to eleven. The following quote illustrates this:

"I have a box with seven compartments in which the medication is stored per day. At the beginning of the week, I organize the medication for the whole week and I expect him to take it. But I do check afterwards. So he takes his medication normally in the morning at breakfast. When I clear the table, I check if the pill is gone. And in the evening, when he's going

to sleep, he takes his medication independently. But I check before he goes upstairs if he took it." (Interview 5, boy of 11 years).

Prevalence of medication nonadherence

Using the BAASIS© Interview, four parents admitted that their child was nonadherent to the immunosuppressive regimen. Using the standard deviations of tacrolimus blood levels, one participant was deemed nonadherent according to the subclinical cut-off point. No participant exceeded the clinical cut-off point. Based on the judgment of the ANP, seven patients were considered to be nonadherent (Table 2. Prevalence of medication nonadherence). Based on the combination of these three criteria, 70% is nonadherent to the immunosuppressive medication based on our operational definition. Using the BAASIS® interview to evaluate adherence to co-medications, two parents admitted to be nonadherent to co-medications (20%).

Barriers

Interviews with the children's parents

Most frequently reported barriers

Table 3 lists all barriers reported per parent, as well as the frequency how often the barrier was mentioned within our sample. Barriers were identified 102 times in the interviews (see Table 6) with a median of ten barriers (range 3-14) per participant (see Table 5). According to the parents, the most predominant barrier is breaking the routine (30%) and a hectic morning (20%).

"It has been like this for years and it becomes a routine. And then you do have the problem that if the routine changes, you'll have to pay attention. Because it could be, when you say for example 'we're going to sleep in', that's the moment you really have to prepare everything beforehand or leave a note. Otherwise, it could be forgotten once in a while." (Interview 5, boy of 11 years).

Some barriers were specifically identified in relationship to ***immunosuppressants***. First of all, the child may sometimes throw up the medication due to coughing, taking the medication too quickly or being too active immediately after intake (30%). When it comes to parents/family/living situation forgetfulness is cited a couple of times (20%), as well as finding a suitable babysitter who can be trusted to give the medication correctly (20%). A lack of flexibility due to the medication regimen has been mentioned as well (20%).

A lot of barriers were expressed in the context of ***medication taking in general***, without making a distinction between immunosuppressants and co-medication. Many of these barriers are identical to the ones identified for immunosuppressants specifically, for example forgetfulness of the parents (50%). This can entail for instance not remembering whether they already gave the child his or her medication, or forgetting to check if the child has indeed taken his or her medication.

"In the long run, it becomes such a routine that you sometimes can't even remember if you have given the medication or not." (Interview 2, girl of 2 years).

Some parents find it hard to let go some of the responsibility and control of the medication (50%). Related to this, they find it difficult to trust others in medication administration, like the babysitter. Especially since forgetfulness of third parties (a teacher or a babysitter) sometimes occurs as well (30%). Lastly, a hectic morning can prove to be difficult as well (30%).

Other barriers concerned the child. Sometimes the child simply refuses the medication because he or she feels ill, is angry or simply doesn't want to take it (40%) or throws it up (20%). This can also be caused by side-effects of the medication like diarrhea, stomach ache or esthetic side-effects (such as excessive hair growth) (30%). Forgetfulness is also identified (20%). A few barriers were mentioned within the medication and medication regimen dimensions. A factor that jumps out again is breaking the routine (50%). This can on the one hand happen due to a change in the medication regimen, either the change of a medication dosage or the adding or elimination of a medication (40%). A lack of flexibility has been mentioned a couple of times as well (20%).

Some barriers reported specifically for ***co-medication*** were the need to administer a painful injection, an earlier negative experience with an injection, and the injection technique is sometimes perceived as difficult (30%).

"When I'm alone, I have to really make sure that I'm holding her leg tight. Because she moves her leg and I have to distract her. It just takes me longer, because of her moving, and sometimes she pushes her leg into the needle but the needle isn't always inserted in the right way. It has to be inserted straight. And then I have the disadvantage that I have to prick her twice. And you have to make sure you're not in a blood vessel. So you have to disinfect the skin, and then you see the white and red spots in her skin better. I have to try to prick in a white spot. Yeah, you have to aim a bit. And then she's moving as well. (Interview 6, girl of 7 years).

The child may sometimes throw up medication as they also do with immunosuppressants (20%), but the reason with co-medication seems to be mainly the medication's bad taste (50%), like for instance antibiotic syrup. Especially medication in a syrup seems to have a bad taste, in comparison to capsules.

"The natrium bicarbonate, when you mix it with grenadine, it becomes black and starts to foam. It's pure salt that you have to take. The easiest way is to mix the powder with a minute soup and then add boiling water. Otherwise it lumps together. In other drinks it really tastes bad and it's hard to get him to take it. The minute soup is quite salty. But he doesn't like all soups. You have to search for solutions." (Interview 7, boy of 6 years).

IMAB

Barriers were identified 77 times in the IMAB with a median of seven barriers (range 2-15) per participant (see Table 5).

Besides the interviews, 22 items from the IMAB are recognized as a barrier by at least one participant. Seven barriers seem not to occur, i.e. getting refills on time, taking so many pills at the same time, not being able to afford the medication, not knowing why he or she needs to take the medication, not understanding when to take the medication, taking the medication when the child feels good, and taking so many tablets each day.

Taking medication when doing other things, taking medication on time because of falling asleep or oversleeping, taking medication when the child feels ill, taking medication when nobody reminds him or her to take it, taking medication when the timing is inconvenient, forgetfulness, and breaking daily routine are identified as a barrier by 50% or more of the participants. Results from the IMAB nicely complement the results from the interviews, although parents seem to report more barriers during the semi-structured interviews. Newly identified barriers not reported during the interview were taking medication when others notice it, not feeling any benefit from the medication, removing the medication from the package, and understanding the instructions on the medication packages (see Table 3).

Facilitators

Most frequently reported facilitators

Table 4 lists all facilitators reported per parent, as well as the frequency how often the facilitator was mentioned within our sample. Facilitators were identified 148 times in the interviews (see Table 7) with a median of 15.5 facilitators (range 6-26) per participant (see Table 6). The most helpful facilitator according to parents seemed to be organization and structure (40%).

Some facilitators were specifically identified in relationship to ***immunosuppressants***, i.e. finding ways to simplify medication intake (30%), followed by having a spare supply of medication at home in a different dosage (20%). Grandparents may ease the burden by babysitting from time to time (20%). Third parties, such as babysitters, are often given oral or written information about the child's condition and his or her medication (20%).

As was the case with the barriers, a lot of facilitators were expressed in the context of ***medication taking in general***. The most frequently reported facilitators referred to the use of practical aids, together with taking medication with you at all times to prevent missing a dosage. All parents named this as a facilitator (100%). Other practical aids are setting an alarm to avoid forgetfulness (70%) and using a medication checklist (60%), a medication box for medication storage (60%), or having a spare supply of medication at home (30%). Having grandparents or another family member as a babysitter is a big help (60%).

"I wouldn't just ask the next door sixteen year old neighbor and say: 'Can you come babysit tonight and oh yeah, at eight o'clock she has to take her Prograft®.' First of all, you can't ask that of someone. Second, I don't want to put that on someone. Look, when it comes to my parents or parents-in-law I just trust them to do that. They have already watched us do it so many times. You explain it to them once and they do it. We ask them to give the Prograft® and leave the rest of the medication or we give that medication before we leave. But basically you have to trust someone completely before you allow anyone to give the medication. Especially something like Prograft®." (Interview 2, girl of 2 years).

Guidance from the healthcare workers is also perceived as helpful, i.e. being taught by the transplant team how to prepare and administer the medication (50%), or a flexible pharmacist in case medication needs to be ordered (50%). A lot of parents find it easier to administer the medications compared to early post-transplant since there are fewer medications to be taken and less experienced medication regimen changes (80%). A couple of parents said that taking medication is a habit for the child. He or she considers it to be normal because he or she has been taking medication practically his or her whole life (60%).

"We are used to it. Medication is a part of X. Just because he started to take medication when he was a couple of months old, he was transplanted at four months. So the immunosuppression etcetera, it's all part of it. Before he could even sit, he was already taking medication." (Interview 5, boy of 11 years).

It also helps to maintain good communication with your child concerning the medication and the need to take it (30%). A couple of helpful ways were mentioned to prepare medication, like preparing the medication in advance (50%). Rituals and structure also play a role: organization and structure seem to be important elements for parents when managing their child's medication regimen (40%).

"From the moment we go out the door, the pills come along. We take them with us automatically. And besides that, I'll tell you, alarms in the cell phone and then we're reminded of the medication. And if we go on vacation or a trip, we have to make sure to take enough supplies along. You have to count for a minute and see whether you're going to have enough medication or not. Or if the pharmacist is going on leave and we've just been on vacation, we need to order four dosages at once. We have to keep that in mind, yeah." (Interview 8, girl of 6 years).

Some other frequently mentioned facilitators are performing a double check as parents: they remind each other of the child's medication (30%), or giving third parties information about the medication, for example giving written or oral information to a babysitter or a teacher when the child is at camp (20%).

The most frequent facilitator when it comes to ***co-medication*** is facilitating medication intake (50%). Examples are breaking the capsule in half so the child can swallow it more easily, countering the medication's bad taste with something that tastes good (f.e. soup, juice, yoghurt), rinsing the child's mouth after taking the medication, and allowing the child to eat something in the morning before he or she takes the medication (because it's hard on the stomach). Some parents indicate that their child prefers to take all capsules at once because they are able to do so and it's less time consuming.

"He is aware of the fact that he has to take the medication and he doesn't protest. That awareness… He is great at that and he should know that too. He takes all the pills at once, in five seconds. It has become part of his life, he realizes that he has to take them and he doesn't make an issue of it." (Interview 1, boy of 10 years).

Attempts are also made to make an injection easier for the child, like distraction during the injection, preparing for the injection, … (30%). Lastly, the ability to change the medication into a form which the child can take more easily was named a couple of times as well, for example a syrup instead of capsules (20%).

Relationship of barriers and facilitators with socio-demographic and clinical variables

Barriers

Table 5 presents the reported barriers per participant and their relationship with the participants' socio-demographic and clinical variables, as well as their self-reported nonadherence, i.e. the child's gender.

The following groups are comparable: gender (female = 50%, male = 50%), the parents' occupational status (both parents work = 40 %, one parent works = 60 %), type of transplantation (kidney transplantation = 50%, liver transplantation = 50%), and sharing responsibility (sharing = 50%, no sharing = 50%). Few parents admit their child being nonadherent, making comparisons in view of number and type of barriers and facilitators is therefore not meaningful (70% is nonadherent, 30% is adherent). Because of skewed groups, no comparisons are based on the parents' marital status

(married or living together = 80%, divorced = 20%), the child's age (age 0-6 years = 30%, age 6-11 years = 70%), and the child's age at transplantation (age at transplant <2 years = 30%, age at transplant >2 years = 70%) either. The following results will be presented using total reported barriers per subgroup instead of medians.

Some groups have notable different barrier totals: nonadherent participants (median 1) report more barriers than adherent participants (median 0), parents of 6 to 11 year old children (median 1) report more barriers than parents of 0 to 6 year old children (median 0), married parents (median 1) report more barriers than divorced parents (median 0), and parents of children transplanted at an age older than 2 years (median 1) report more barriers than parents of children transplanted at an age of younger than 2 years (median 0). No notable differences in total barriers can be observed based on gender (both median 1), the parents' occupational status (both median 1), type of transplantation (both median 1), and the sharing of responsibility (both median 1).

Some barriers specifically display a great difference between groups: the parents' forgetfulness is named by 75% of married parents and 50% of divorced parents. The child throwing up medication is named by 33.3% of adherent patients and 85.7% of nonadherent patients, by 33.3% in children from 0 to 6 years old and 85.7% in children from 6 to 11 years old, and 33.3% in children younger than 2 years at transplantation and 85.7% of children older than 2 years at transplantation.

Similar to the interviews, nonadherent participants (median 3) report more barriers than adherent participants (median 1) on the IMAB score, as well as married parents (median 3) compared to divorced parents (median 0). Inconvenient medication intake moments is the only barrier in the IMAB to display a great difference between groups: it's named by 75% of married parents and 50% of divorced parents, and by 25% of families with both parents working and by 100% of families with one parent working.

Facilitators

Table 6 presents the reported facilitators per participant and their relationship with the participants' socio-demographic and clinical variables.

Some groups have notable different facilitator totals: nonadherent participants (median 1) report more facilitators than adherent participants (median 0), parents of boys (median 1) report more facilitators than parents of girls (median 1), parents of children age 6 to 11 years (median 1) report more facilitators than parents of children 0 to 6 years (median 0), married parents (median 1) report more facilitators than divorced parents (median 1), and parents of children older than 2 years at transplantation (median 1) report more facilitators than parents of children younger than 2 years at transplantation (median 0). No notable differences have been found in type of transplantation (both median 1) and the sharing of responsibility (both median 1).

Taking medication with you when going out is named by 100% of adherent patients and 100% of nonadherent patients, and by 100% of married parents and 100% of divorced parents. Setting an alarm is named by 33.3% of adherent patients and 85.7% of nonadherent patients, and by 75% of married parents and 50% of divorced parents. Using a medication box

isn't named in children age 0 to 6 years, in contrast to 85.7% in children age 6 to 11 years. It isn't named in children younger than 2 years at transplantation either and 85.7% in children older than 2 years at transplantation. Having a flexible pharmacist isn't named in children age 0-6 years, while it's named 71.4% in children age 6 to 11 years. It isn't named either in children younger than 2 years at transplantation and 71.4% in children older than 2 years at transplantation. Simplifying intake isn't named in children age 0 to 6 years in contrast to 100% in children 6 to 11 years. It isn't named either in children younger than 2 years at transplantation and 100% in children older than 2 years at transplantation. Lastly, preparing medication in advance isn't named in children age 0 to 6 years and 71.4% in children age 6 to 11 years, as is the case in children younger than 2 years at transplantation compared to children older than 2 years at transplantation.

DISCUSSION

In this research we aimed to answer two main research questions, first the prevalence of medication nonadherence to immunosuppressants and co-medication in pediatric liver and kidney transplantation patients. Second, positive and negative influencing factors of medication taking. This study is the first study to research these matters in a strictly pediatric sample. Other studies tend to have a mixed sample, despite younger children and adolescents experiencing different barriers. No literature to date exists that focuses not only on barriers, but also on facilitators and that links them to socio-demographic and clinical data. Considering these aspects, this study is quite innovative.

A total of 70% of participants was nonadherent to immunosuppressant medication, of which 40% are liver transplantations and 30% kidney transplantations. The prevalence of medication nonadherence in kidney transplantations corresponds with previous findings (30-32%), while we found a slightly higher percentage in liver transplantations (17-32%) (4-10). Twenty percent of participants was nonadherent to co-medication. Parents admit to more nonadherence in the depth interview than they score in the BAASIS© interview. They are generally strict with immunosuppressants because of their 'vital importance', and less so in co-medication, which they considered less important. Healthcare workers should emphasize the importance of co-medications within the medication regimen more. Patients either took Prograft® (90%) or Neoral® (10%) as a basic immunosuppressive therapy. To assess mediation adherence, we used a three-way evaluation method to provide triangulation: the BAASIS© interview, an ANP judgment and standard deviations calculated from immunosuppressive blood levels. We didn't calculate standard deviations of cyclosporine blood levels since few evidence exists concerning its blood level reliability. The patient that didn't have a calculated standard deviation scored nonadherent in the other two methods, so the blood level was in this case not a critical component. There's still much discussion about cut-off points of standard deviations calculated from tacrolimus blood levels. Shemesh and Fine (2010) state that cut-off points range from 2 to 3.5 (19). We used 2 as a subclinical cut-off point and 3.5 as a clinical cut-off point in this study. The reliability of tacrolimus blood levels is considered good (19).

Parents seemed to attribute some barriers specifically to immunosupressants or co-medication, while some barriers were stated generally. More barriers regarded co-medication specifically, especially the medication's bad taste. This occurs less in immunosuppressants, since they're generally capsules. Some barriers were only mentioned in immunosuppressants or only in co-medication. The reason for certain differences aren't clear, for example preparation seems to cause barriers in

co-medication and not in immunosuppressants. Do parents have more knowledge concerning immunosuppressants since they are vitally important medications or do parents find their preparation simply easier than co-medication?
Our systematic review (Claes et al. 2011) states that parents and children indicate the child's forgetfulness as the most frequent reason for medication nonadherence. We find the parents' forgetfulness to be the most frequent barrier (70%) with a lower frequency of the child's forgetfulness (30%). This is due to the parents taking the majority of medication responsibility and a difference in median sample age and range. The child's forgetfulness rate corresponds with previous findings, while we observe a higher rate of the parent's forgetfulness. Some barriers were reported in other studies while they didn't come forward in ours: the child being angry with his or her parents, the child thinking he or she doesn't need medication, medication intake is time consuming, and medication intake reminds the child of being ill. Some barriers did correspond: the medication's bad taste, and its side-effects (10). Percentages differ because of our relatively small sample in comparison other studies. According to the review, medication nonadherence is also significantly related to limitations in social and school activities related to emotional and behavioral problems. Besides that, it was also related to the parents' emotional functioning, family cohesion, health related quality of life and health status (frequency of hospital admissions, length of hospital stay, number of liver biopsies and number of rejections) (10). These are aspects that weren't researched in our study. We can't draw any conclusions concerning the family cohesion, 80% of parents in our sample were married or living together and only 20% was divorced.
Recognized barriers in the IMAB and the interviews complement each other well. Parents sometimes recognized barriers in the IMAB while they didn't mention them in the interview, but overall parents identified more and different kinds of barriers compared to the IMAB. The IMAB is based on an adult population and aims to evaluate barriers related to immunosuppressants solely. We used it to evaluate medication in general to include co-medication and to question barriers that parents as well as their child may experience.

We researched present barriers in our study, but parents also reported a lot of past barriers, mostly concerning the early post-transplant period when they had to deal for example with more medications, regimen changes and the child's inability to swallow capsules. Parents seem to experience more and different kinds of barriers in the past and feel more need to implement facilitators. We need to examine these differences and why they occur, if parents experience less barriers presently or if they acquire more facilitators over time and/or learn how to better use them?

Parents reported practical matters most frequently, such as setting an alarm to prevent forgetfulness or having a medication box. All parents without exception identified taking medication with them when going out as a facilitator. In contrast to barriers, facilitators were more often reported specifically in relationship to immunosuppressants. Facilitators seem to mirror barrier as parents who reported more barriers also utilized more facilitators. For example nonadherent patients also tried a lot of aspects to be adherent. There isn't any evidence that specifically researches facilitators, but some studies do mention effective strategies that improve medication adherence. De Bleser et al. (2010) advise in their systematic review to combine interventions in a team approach to improve adherence. Reported interventions are patient-focused, cognitive/educational, counseling/behavioral, psychological/affective, and also relate to the healthcare provider/setting/system. More research is still needed to determine the most effective intervention combination (23).

When comparing barriers and facilitators to socio-demographic and clinical variables, we noticed that some subgroups weren't comparable. This made it difficult to correctly present results: presenting total numbers would complicate their

interpretation and lead to a distorted interpretation while medians take sample size into account. While totals seemed to have some notable differences, medians were small. This could be due to the numerous barriers and facilitators that were named by only one patient. Or it could mean that differences between subgroups simply aren't that great.

Parents in general appear to not think too deeply about the medication and (non)adherence. A lot of them said when asked to participate in the study or when starting the interview that everything is fine. But when questioning them, they did report quite a few barriers. Most of them considered their adherence as (very) good, while the ANP considered half of them as nonadherent. When they were asked about facilitators, they were hesitant at first and had difficulty identifying them. Parents need to dwell a bit more with possible barriers and facilitators which might influence medication adherence. We do have to keep a possible bias in mind, since parents may have presented themselves in a more positive way because they were interviewed. Presenting parents with more information and advice may proof beneficial.

This study has certain limitations. It's a monocentric study conducted in a university Hospital in Belgium, which may mean specific characteristics of the centre, culture, and Belgian healthcare system are represented in the results. The sample was limited to children up to eleven years who had a liver or kidney transplantation. The results can therefore not be generalized to a broader, Western context or to other age groups. Eight out of eighteen patients declined participation: almost half of contacted participants. Saturation of data may not have been completely reached, although it seems that parents generally recognize the same barriers and facilitators. The IMAB as an instrument wasn't completely validated. There are also no existing instruments that measure facilitators, so there wasn't any quantitative data concerning facilitators to complete the qualitative data. This qualitative study might form the basis to on the one hand fine tune the IMAB. It needs to be adjusted to a pediatric population with, aiming at all medications and provide a differentiation in barriers concerning the parents and the child. It should also be assessed to determine whether it concludes all relevant barriers. On the other hand, it's a start to develop an instrument to measure facilitators towards medication taking quantitatively.

This study nevertheless might have some important implications for clinical practice and further research:

- Current existing instruments that aim to identify barriers concerning medication intake (such as the IMAB and the BAASIS© Interview) need to be adjusted so they don't solely focus on immunosuppressants but also at co-medication. They should also differentiate between barriers experienced by parents and those experienced by the child itself, since the medication responsibility lies mostly with the parents or is shared with the child.
- Instruments should be designed that identify facilitators concerning medication intake, since no instruments exist yet that do this.
- Support groups for parents of transplant children need to be further organized. Parents take comfort in the fact that they can talk to others who are in an identical situation. Other than that, they can also learn from each other (tricks, tips). They get access to different, but equally useful information this way.
- More research is needed to investigate facilitators concerning medication intake. Literature focuses exclusively on barriers, while facilitators are equally important.
- Most studies don't have a strictly pediatric (0 to 12 years) sample. We need more studies that focus on younger children and make a distinction between different age groups.

- This study focused on barriers and facilitators that parents experience in the present, but past barriers and facilitators (especially early-post-transplant) need to be further explored.
- There are several ways to evaluate medication adherence: blood levels, clinical impressions, self reports. Blood levels are very individual and sometimes questionable in reliability. Some healthcare workers prefer to rely on clinical impressions and self reports. We need to further conduct comparative studies to evaluate these methods and determine which one or which combination is superior.
- Parents report differences between adherence to immunosuppressant medication and co-medication. We need to investigate these differences and the underlying reasons.

CONCLUSION

This study provides innovative information concerning medication nonadherence in pediatric liver and kidney transplantation. First of all, because it applies to a strictly pediatric sample, which previous studies haven't done. Furthermore, it differentiates between medication nonadherence to immunosuppressants and co-medication. Not only barriers, but also facilitators are investigated (which have been overlooked unjustly in previous studies) and related to the participants' socio-demographic and clinical characteristics. This study offers new evidence which can prove very useful in the guidance of this particular patient population, and is a start to more profound research.

ETHICAL CONSIDERATIONS

This Master's thesis has been approved by the ethical and judging commission Master's thesis Nursing and Midwifery of the Katholieke Universiteit Leuven. The University Hospitals of Leuven has granted permission to execute this research project within this institution. Research participants don't receive any direct benefits or disadvantages by their participation. The research goal and all conditions are explained in the written informed consent form, so the participants receive all information in writing and written consent can be given. They receive individual oral information concerning the research and potential questions are answered by the student researcher (Claes). The parents need to sign the written informed consent form since they are legally responsible for their child. Participants are assured of the voluntary nature of the research and that they can withdraw their consent at any time without having to give an explanation. All data are coded and handled with complete anonymity. The interview tapes are only available to the interviewer and will be destroyed after processing. Participant anonymity is guaranteed as much as possible this way.

AUTHOR CONTRIBUTIONS

This Master's thesis was executed and written by Anouck Claes, with great guidance and support from Prof. Dr. Fabienne Dobbels, Mrs. Loes Decorte and Prof. Dr. Elena Levtchenko. This especially in terms of designing the research design and research methods, data analysis and statistical processing of the results, writing the article, critical evaluation and approving of the final article.

RECOGNITIONS

This Master's thesis has been executed in the context of the education 'Master of Science in Nursing and Obstetrics' and is the result of cooperation with the Katholieke Universiteit Leuven (Leuven, Belgium).

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TABLES

Table 1. Socio-demographic and clinical variables of transplanted children (n=10)

Gender (n)	
Boy	5 (50%)
Girl	5 (50%)
Age (years, median[a], range)	6.5 (2-11y)
0-6y (n)	3 (30%)
6-11y (n)	7 (70%)
Transplantation (n)	
Kidney (n)	5 (50%)
Non cadaveric donor	1 (10%)
Cadaveric donor	4 (40%)
One kidney	4 (40%)
Two kidneys	1 (10%)
Liver (n)	5 (50%)
Non cadaveric donor	3 (30%)
Cadaveric donor	2 (20%)
Whole lever	2 (20%)
Part lever	3 (30%)
Age at transplantation (years, median, range)	1 (4m-5y)
Age at Tx <2y (n)[b]	3 (30%)
Age at Tx >2y (n)	7 (70%)
Earlier transplantation (n)	
Yes	1 (10%)
No	9 (90%)
Occupational status parents (n)	
Both parents work	4 (40%)
One parent doesn't work	6 (60%)
Marital status (n)	
Married or living together	8 (80%)
Divorced/other	2 (20%)
Family composition (n)	
Only child	5 (50%)
One sibling	3 (30%)
Three or more siblings	2 (20%)
Amount of medication intake (median, range)	5.5 (2-11)
Immunosuppressants (median, range)	1.5 (1-3)
Co-medication (median, range)	3.5 (1-10)

[a] Median is used instead of mean because of the small sample size

[b] Tx = transplantation

Table 2. Prevalence of medication nonadherence

Patient	1-BAASIS© interview											2-Blood levels[d]		3-ANP	TOTAL[f]
	A) Taking NA[a]		*B) Drug holidays*		*C) Timing NA*		*D) Dosage NA*		*Total NA*		NA[c] (Yes/ no)	SD	SD >2	NA (yes/ no)	NA (yes/ no)
	IS[b]	CM	IS	CM	IS	CM	IS	CM	IS	CM					
1	0	0	0	0	1	0	0	0	1	0	Y	1.517	N	Y	**Y**
2	0	0	0	0	0	0	0	0	0	0	N	0.837	N	N	**N**
3	0	0	0	0	0	0	0	0	0	0	N	/[e]	/	N	**N**
4	1	0	0	0	1	0	0	0	1	0	Y	2	Y	Y	**Y**
5	0	0	0	0	1	0	0	0	1	0	Y	0.548	N	N	**Y**
6	0	0	0	0	0	0	0	0	0	0	N	0.548	N	N	**N**
7	0	1	0	0	0	0	0	0	0	1	Y	0.894	N	Y	**Y**
8	0	1	0	0	0	0	0	0	0	1	Y	1.225	N	N	**Y**
9	0	0	0	0	0	0	0	0	0	0	N	1.483	N	Y	**Y**
10	0	0	0	0	1	0	0	0	0	0	Y	0.447	N	Y	**Y**
Total	1	1	0	0	1	0	0	0	4	2	6		1	5	
															7

[a] NA = nonadherence

[b] IS = immunosuppressants; CM = co-medication
1 = nonadherent; 0 = adherent

[c] Nonadherence in at least 1 out of 4 items is considered as nonadherent

[d] A SD of≥ 2 is considered as nonadherent

[e] A standard deviation wasn't calculated from cyclosporine blood levels

[f] Scoring 'yes' in at least 1 out of 3 items is considered as nonadherent

Table 3. Reported barriers

Barrier dimension	Reported barriers	Number of parents reporting barrier (%)		
		Total[a]	IS[b]	CM
Parents / family / living situation	Forgetfulness	7 (70%)	2 (20%)	/
	Letting go of responsibility/control	5 (50%)		
	Finding a suitable babysitter	3 (30%)	2 (20%)	
	Forgetfulness of third parties	3 (30%)		
	A hectic morning	3 (30%)		
	Parents are insecure, especially early post transplantation	2 (20%)		
	Parent fear or dislike giving an injection/don't want to force intake	2 (20%)		
	Not having refills on time	2 (20%)		
	The cost of medication and medication supplies	2 (20%)		
	The pharmacist prepared the wrong medication dosage	1 (10%)	1 (10%)	
	Parents gave the wrong dosage due to a miscommunication with their treating physician	1 (10%)	1 (10%)	
	Being home too late to give the medication	1 (10%)	1 (10%)	
	A reward after each injection isn't feasible	1 (10%)		1 (10%)
	The medication regimen can become a habit	1 (10%)		
	Being divorced	1 (10%)		
	A single mother with a father who doesn't want to be involved	1 (10%)		
	Multiple children with a chronic illness and medication	1 (10%)		
	Limited communication/continuity due to multiple physicians	1 (10%)		
	Taking material everywhere to prepare medication anywhere	1 (10%)		
	Transportation to the hospital	1 (10%)		
Medication preparation / administration	Having to give an injection	3 (30%)	/	3 (30%)
	Medication mixed with f.e. yoghurt means the child has to eat the whole thing to take the complete dosage	1 (10%)		1 (10%)
	A miscommunication about how to prepare medication	1 (10%)		
	A syringe delivered with a medication isn't that easy to clean	1 (10%)		
	Not being able to prepare medication in advance in a syringe	1 (10%)		
The child	Throwing up medication	7 (70%)	3 (30%)	2 (20%)
	Refusing medication	4 (40%)		
	Forgetfulness	3 (30%)		1 (10%)
	Dealing with the consequences of having a kidney or liver transplant	2 (20%)		
	A second pathology	2 (20%)		
	An 'It's not fair feeling' towards others (siblings, peers)	2 (20%)		
	Sleepiness at the moment of medication intake	2 (20%)		
	Hard to swallow capsules (f.e. due to a young age)	1 (10%)		1 (10%)
	Being occupied with something else	1 (10%)		
	Pulling away his or her leg during an injection	1 (10%)		
Medication regimen	Breaking the routine	5 (50%)	/	/
	Lack of flexibility	4 (40%)	2 (20%)	
	Changes in the medication regimen and amount of medications	4 (40%)		

	Medication has to be taken a specific way (f.e. sober in the morning)	1 (10%)		1 (10%)
	Breaking the routine due to additional medication, not related to the transplantation (f.e. when the child has the flu)	1 (10%)		
	Having to take multiple medications at once	1 (10%)		
Medication characteristics	A bad taste	6 (60%)	1 (10%)	5 (50%)
	Side effects (diarrhea, stomach ache, esthetic such as hair growth)	3 (30%)		
	A strange texture	1 (10%)		1 (10%)
	The size of the capsule is too big	1 (10%)		
	The amount of medication is too large (in ml)	1 (10%)		
Medication storage	Medication needs to be stored at a low temperature	2 (20%)	/	/

[a] Total = most frequent barrier in total, without distinction between IS, CM and general

[b] IS = immunosuppressants; CM = co-medication

Table 4. Reported facilitators

Facilitator dimension	Reported facilitators	Number of parents reporting facilitator (%)		
		Total[a]	IS[b]	CM
Aids at home	Taking medication with you at all times	10 (100%)		
	An alarm	7 (70%)	1 (10%)	/
	Medication list	6 (60%)		
	A medication box	6 (60%)	1 (10%)	1 (10%)
	A spare supply of medication at home	3 (30%)	1 (10%)	1 (10%)
	Having a spare supply at home in a different dosage	2 (20%)	2 (20%)	
	A medication cabinet	2 (20%)		
	A cooling bag	2 (20%)	1 (10%)	1 (10%)
	Highlighting changes in the schedule	2 (20%)		
	Each chronically ill family member has a medication box	2 (20%)		
	A scribble	1 (10%)		
	Making your own medication schedule	1 (10%)		
External help	Having grandparents or other family members as babysitter	6 (60%)	2 (20%)	
	Guidance from healthcare workers	5 (50%)		/
	A flexible pharmacist	5 (50%)		
	The pharmacist can provide the medication in a different form (f.e. each pill in different colors or a syrup instead of a capsule)	2 (20%)		
	A flexible general practitioner	1 (10%)		
	The teacher can give the medication at school	1 (10%)		
	Arranging individual transportation to school because of timing issues in the morning	1 (10%)		
Medication intake / administration	Making medication intake easier	7 (70%)	3 (30%)	5 (50%)
	Making an injection easier	3 (30%)		3 (30%)
	Placing medication on the dinner table so the child sees it	2 (20%)		
	Teaching the child in a playful way	1 (10%)		
	Being strict if needed and aware of the child's (in)capabilities	1 (10%)		
Medication (regimen) characteristics	Less medications and changes in the medication regime	8 (80%)		
	Changing medication form which the child can take more easily	3 (30%)	1 (10%)	2 (20%)
	A good taste	1 (10%)		1 (10%)
	A transition to capsules (which have no taste)	1 (10%)		
	A small amount of medication (in ml)	1 (10%)	1 (10%)	
	The ability to move medication intake a little bit	1 (10%)	1 (10%)	1 (10%)
	The ability to plan an injection-free day (when 6 out of 7 days an injection has to be administered)	1 (10%)		1 (10%)
	Changing medication form so it can be obtained from any pharmacist	1 (10%)		
	When using capsules, parents don't have to deal with milliliters	1 (10%)		
The child	Taking medication is a habit, the child experiences it as normal	6 (60%)	/	/
	Good communication with the child	3 (30%)		
	The child simply takes the medication well	2 (20%)		
	The child accepts the medication and realizes its chronic nature	2 (20%)		
	Letting the child cool off if he or she is angry	2 (20%)		
	The ability to swallow capsules	2 (20%)		
	Trust in his or her parents	1 (10%)		
	Not allowing the child to become too active right after intake	1 (10%)	1 (10%)	

	The child grows older and more mature	1 (10%)		1 (10%)
Medication preparation	Preparing medication in advance	5 (50%)	/	/
	Paying attention and being alert when preparing medication	2 (20%)		
	Using prepackaged sterile syringes to keep hygiene in mind	1 (10%)		
	Only leaving the medication in the medication box that the grandparents have to give as babysitters to prevent mistakes	1 (10%)		
A ritual / structure	Organization and structure	4 (40%)	/	/
	Holding on to a certain routine & maintaining rituals	1 (10%)		
A reward	Offering the child a reward after a hospital visit	1 (10%)	/	/
Other	Reminding each other as parents; a double check	4 (40%)	1 (10%)	
	Giving information to third parties (f.e. babysitter)	4 (40%)	2 (20%)	
	Gaining knowledge from other parents (f.e. parent association)	2 (20%)		
	Parents have knowledge about the transplantation	1 (10%)		
	Gaining information from the internet (f.e. tricks or advice)	1 (10%)		
	Less confusion about who gave the medication when divorced	1 (10%)	1 (10%)	
	In case of a sleepover with a friend, calling his or her mother when it's time to take the medication	1 (10%)		
	Good communication with ex-husband or ex-wife	1 (10%)		

[a] Total = most frequent facilitator in total, without distinction between IS, CM and general

[b] IS = immunosuppressants; CM = co-medication

Table 5. Reported barriers & relationship with demographic and clinical variables

BARRIERS (n = 47+9)	BARRIERS PER PARTICIPANT											BARRIERS IN RELATIONSHIP TO DEMOGRAPHIC AND CLINICAL VARIABLES															
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	TOTAL	Adherent (n=3)	Nonadherent (n=7)	Female (n=5)	Male (n=5)	0-6 y old (n=3)	6-11 y old (n=7)	Married (n=8)	Divorced (n=2)	2 parents work (n=4)	1 parent works (n=6)	Age at Tx < 2 y (n=3)[e]	Age at Tx > 2 y (n=7)	Kidney Tx (n=5)	Liver Tx (n=5)	Shared resp. (n=5)	No shared resp. (n=5)
Forgetfulness parents		x		x	x	x		x	x	x	**7**	**2**[d]	**5**	4	3	3	4	**6**	**1**	**2**	**5**	**2**	**5**	3	4	**2**	**5**
Letting go of control	x		x		x			x	x		**5**	**1**	**4**	2	3	2	3	**4**	**1**	2	3	**1**	**4**	**4**	**1**	3	2
Suitable babysitter		x	x				x				**3**	**2**	**1**	2	1	1	2	2	1	1	2	1	2	1	2	2	1
Forgetfulness 3[d] parties	x		x			x					**3**	**2**	**1**	2	1	**0**	**3**	**3**	**0**	2	1	**0**	**3**	**3**	**0**	2	1
Hectic morning	x				x				x		**3**	**0**	**3**	**0**	**3**	1	2	2	1	1	2	1	2	2	1	2	1
Parents are insecure				x					x		**2**	0	2	0	2	1	1	2	0	0	2	1	1	1	1	1	1
Parents dislike hurting child							x		x		**2**	0	2	0	2	1	1	1	1	1	1	1	1	1	1	1	1
Not having refills on time				x	x						**2**	0	2	0	2	0	2	1	1	0	2	0	2	0	2	2	0
Cost medication/material				x				x			**2**	0	2	1	1	0	2	2	0	1	1	0	2	1	1	1	1
Wrong dosage pharmacist				x							**1**	0	1	0	1	0	1	1	0	0	1	0	1	0	1	1	0
Wrong dosage physician								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Home too late									x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	0	1
Reward after injection	x										**1**	0	1	0	1	0	1	1	0	1	0	0	1	1	0	1	0
Medication is a habit				x							**1**	0	1	0	1	0	1	1	0	0	1	0	1	0	1	1	0
Divorced							x				**1**	0	1	0	1	0	1	0	1	1	0	0	1	0	1	1	0
Father isn't involved					x						**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Multiple ill children					x						**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Multiple physicians								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Taking material with you				x							**1**	0	1	0	1	0	1	1	0	0	1	0	1	0	1	1	0
Transportation to hospital					x						**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
An injection	x					x	x				**3**	**1**	**2**	1	2	**0**	**3**	2	1	**3**	**0**	**0**	**3**	2	1	2	1
Mixing with good taste							x				**1**	0	1	0	1	0	1	0	1	1	0	0	1	0	1	1	0
Prepare miscommunication								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Syringe difficult to clean								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Can't prepare in advance								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Throws up medication	x			x	x	x	x	x		x	**7**	**1**	**6**	3	4	**1**	**6**	**5**	**2**	4	3	**1**	**6**	3	4	4	3
Refuses medication	x	x						x	x		**4**	**1**	**3**	2	2	2	2	**4**	**0**	2	2	2	2	3	1	1	3
Forgetfulness child	x		x		x						**3**	1	2	1	2	**0**	**3**	2	1	1	2	**0**	**3**	2	1	**3**	**0**
Consequences of transplant			x						x		**2**	1	1	1	1	1	1	2	0	0	2	1	1	2	0	1	1

Second pathology			x			x					**2**	2	0	2	0	0	2	2	0	1	1	0	2	2	0	1	1
'It's not fair' feeling			x		x						**2**	1	1	1	1	0	2	1	1	0	2	0	2	1	1	2	0
Sleepiness	x			x							**2**	0	2	0	2	0	2	2	0	1	1	0	2	1	1	2	0
Hard swallow medication						x					**1**	1	0	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Occupied with something	x										**1**	0	1	0	1	0	1	1	0	1	0	0	1	1	0	1	0
Pulls leg away - injection						x					**1**	1	0	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Breaking the routine	x	x		x	x	x					**5**	**2**	**3**	2	3	**1**	**4**	**4**	**1**	2	3	**1**	**4**	2	3	3	2
Lack of flexibility		x	x			x		x			**4**	**3**	**1**	**4**	**0**	1	3	**4**	**0**	2	2	1	3	3	1	2	2
Changes in medication	x	x		x	x						**4**	1	3	1	3	1	3	3	1	1	3	1	3	1	3	3	1
Medication in a certain way		x									**1**	1	0	1	0	1	0	1	0	0	1	1	0	0	1	0	1
Additional medication								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Multiple medications in 1x		x									**1**	1	0	1	0	1	0	1	0	0	1	1	0	0	1	0	1
Bad taste	x		x	x			x	x	x		**6**	**1**	**5**	2	4	**1**	**5**	**5**	**1**	3	3	**1**	**5**	4	2	4	2
Side-effects			x					x		x	**3**	**1**	**2**	**3**	**0**	1	2	**3**	**0**	1	2	1	2	2	1	1	2
Strange texture								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Capsules too big	x										**1**	0	1	0	1	0	1	1	0	1	0	0	1	1	0	1	0
Amount too large (in ml)							x				**1**	0	1	0	1	0	1	0	1	1	0	0	1	0	1	1	0
Storage at low temperature		x					x				**2**	1	1	1	1	1	1	1	1	1	1	1	1	0	2	1	1
Total interview barriers	**14**	**9**	**11**	**12**	**12**	**9**	**9**	**14**	**9**	**3**	**102**	**28**	**74**	**46**	**56**	**22**	**80**	**81**	**21**	**47**	**55**	**20**	**82**	**57**	**45**	**58**	**44**
Median per subgroup											*1*	*0*	*1*	*1*	*1*	*0*	*1*	*1*	*0*	*1*	*1*	*0*	*1*	*1*	*1*	*1*	*1*
IMAB in interviews[a]	5	5	3	5	5	1	1	5	4	3	37																
Multiple times a day	x	x							x		**3**	**1**	**2**	1	2	2	1	**3**	**0**	1	2	2	1	2	1	1	2
Removing from package								x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Others notice	x									x	**2**	0	2	1	1	1	1	2	0	1	1	1	1	1	1	1	1
Hard to take if going out	x	x		x		x					**4**	2	1	2	2	1	3	**4**	**0**	2	2	1	3	2	2	2	2
Not feeling benefit	x								x		**2**	0	2	0	2	1	1	2	0	1	1	1	1	2	0	1	1
Instructions package	x										**1**	0	1	0	1	0	1	1	0	1	0	0	1	1	0	1	0
Inconvenient moments	x	x	x	x	x				x	x	**7**	**2**	**5**	3	4	3	4	**6**	**1**	**1**	**6**	3	4	3	4	3	4
Child feels sad/depressed	x						x			x	**3**	**0**	**3**	1	2	1	2	2	1	2	1	1	2	1	2	2	1
Hard to go out		x	x			x					**3**	**3**	**0**	2	1	1	2	**3**	**0**	1	2	1	2	2	1	**0**	**3**
IMAB not in interviews[b]	7	4	2	2	1	2	1	1	3	3	26	**8**	**17**	**11**	**15**	**10**	**16**	**24**	**2**	**11**	**15**	**10**	**16**	**15**	**11**	**11**	**15**
Total IMAB barriers[c]	**15**	**11**	**9**	**9**	**7**	**3**	**2**	**7**	**7**	**7**	**77**	**14**	**54**	**32**	**36**	**24**	**44**	**62**	**6**	**26**	**42**	**23**	**45**	**37**	**31**	**33**	**35**
Median per subgroup											*2*	*1*	*3*	*1.5*	*2*	*1*	*2*	*3*	*0*	*1*	*2*	*1*	*2*	*2*	*1*	*1.5*	*2*

[a] IMAB barriers also identified in interviews (marked by **green bold numbers**)

[b] IMAB barriers not identified in interviews

[c] Total IMAB barriers may differ from the sum of IMAB barriers identified in interviews and those not identified in interviews as some IMAB items are fairly similar and may be mentioned as 1 item in the interview

[d] Differences in barriers between groups are marked by **red bold numbers**

[e] Tx = transplantation

Table 6. Reported facilitators & relationship with demographic and clinical variables

FACILITATORS (n = 57)	FACILITATORS PER PARTICIPANT											FACILITATORS IN RELATIONSHIP TO DEMOGRAPHIC AND CLINICAL VARIABLES															
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	TOTAL	Adherent (n=3)	Nonadherent (n=7)	Female (n=5)	Male (n=5)	0-6 y old (n=3)	6-11 y old (n=7)	Married (n=8)	Divorced (n=2)	2 parents work (n=4)	1 parent works (n=6)	Age at Tx < 2 y (n=3)[b]	Age at Tx > 2 y (n=7)	Kidney Tx (n=5)	Liver Tx (n=5)	Shared resp. (n=5)	No shared resp. (n=5)
Taking medication with you	x	x	x	x	x	x	x	x	x	x	**10**	**3**	**7**	4	6	**3**	**7**	**8**	**2**	4	6	**3**	**7**	5	5	5	5
Alarm	x			x	x	x		x	x	x	**7**	**1**	**6**	**2**	**5**	**2**	**5**	**6**	**1**	3	4	**2**	**5**	4	3	3	4
Medication list	x		x	x		x	x		x		**6**	**2**	**4**	**1**	**5**	**1**	**5**	**5**	**1**	3	3	**1**	**5**	4	2	4	2
Medication box	x		x	x	x		x	x			**6**	**1**	**5**	2	4	**0**	**6**	4	2	3	3	**0**	**6**	3	3	**5**	**1**
Spare supply at home		x				x				x	**3**	**2**	**1**	**3**	**0**	1	2	**3**	**0**	1	2	2	1	1	2	**0**	**3**
Spare supply (≠ dosage)				x	x						**2**	0	2	0	2	0	2	1	1	0	2	0	2	0	2	2	0
Medication cabinet		x							x		**2**	1	1	1	1	2	0	2	0	0	2	2	0	1	1	0	2
Cooling bag		x					x				**2**	1	1	1	1	1	1	1	1	1	1	1	1	0	2	1	1
Highlighting changes list	x						x				**2**	0	2	0	2	0	2	1	1	2	0	0	2	1	1	2	0
Separate medication boxes					x			x			**2**	0	2	1	1	0	2	1	1	1	1	0	2	1	1	1	1
Scribble					x						**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Making own schedule					x						**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Family members babysit	x			x	x	x		x		x	**6**	**1**	**5**	2	4	**1**	**5**	**5**	**1**	3	3	**1**	**5**	3	3	2	4
Guidance healthcare team		x		x	x	x	x		x		**6**	**2**	**4**	**1**	**5**	**1**	**4**	3	2	2	3	**1**	**4**	2	3	3	1
Flexible pharmacist	x				x	x	x	x			**5**	**1**	**4**	**1**	**4**	**0**	**5**	3	2	**4**	**1**	**0**	**5**	3	2	3	2
Other form (pharmacist)					x				x		**2**	0	2	0	2	1	1	1	1	0	2	1	1	1	1	1	1
Flexible physician					x						**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Teacher gives medication							x				**1**	0	1	0	1	0	1	0	1	1	0	0	1	0	1	1	0
Individual school transport									x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	0	0
Simplifying intake	x		x	x	x	x	x	x			**7**	**2**	**5**	**2**	**5**	**0**	**7**	**5**	**2**	4	3	**0**	**7**	4	3	**5**	**2**
Simplifying injection	x					x	x				**3**	**1**	**2**	**0**	**3**	**0**	**3**	2	1	**3**	**0**	**0**	**3**	2	1	2	1
Medication on dinner table	x				x						**2**	0	2	0	2	0	2	1	1	1	1	0	2	1	1	2	0
Teaching the child playfully									x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	1	0
Being strict									x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	1	0
Less medications/changes		x	x	x	x	x	x	x		x	**8**	**3**	**5**	4	4	**2**	**6**	**6**	**2**	3	5	**2**	**6**	3	5	4	4
Other form (easier intake)		x						x	x		**3**	**1**	**2**	2	1	2	1	**3**	**0**	1	2	2	1	2	1	**0**	**3**
Good taste		x									**1**	1	0	1	0	1	0	1	0	0	1	1	0	0	1	0	1
Capsules (no taste)				x							**1**	0	1	0	1	0	1	1	0	0	1	0	1	0	1	1	0
Small amount (in ml)						x					**1**	1	0	1	0	0	1	1	0	1	0	0	1	1	0	0	1

Moving medication timing									x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Injection-free day							x					**1**	1	0	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Other form-any pharmacist										x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	0	1
Capsules = no ml										x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	0	1
Medication is a habit (child)	x	x		x	x	x		x				**6**	**2**	**4**	3	3	**1**	**5**	**5**	**1**	3	3	**1**	**5**	3	3	4	2
Communication child			x		x					x		**3**	**1**	**2**	1	2	1	2	2	1	**0**	**3**	1	2	2	1	2	1
Child takes medication well		x		x								**2**	1	1	1	1	1	1	2	0	0	2	1	1	0	2	1	1
Child accepts medication	x		x									**2**	1	1	1	1	0	2	2	0	1	1	0	2	2	0	2	0
Letting the child cool off	x		x									**2**	1	1	1	1	0	2	2	0	1	1	0	2	2	0	2	0
Ability to swallow				x					x			**2**	0	2	1	1	0	2	2	0	1	1	0	2	1	1	1	1
Trust in parents	x											**1**	0	1	0	1	0	1	1	0	1	0	0	1	1	0	1	0
Not too active after intake						x						**1**	1	0	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Child is older, more mature						x						**1**	1	0	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Preparing in advance	x		x	x	x				x			**5**	**1**	**4**	2	3	**0**	**5**	**4**	**1**	2	3	**0**	**5**	3	2	**4**	**1**
Alert during preparation	x				x							**2**	0	2	0	2	0	2	1	1	1	1	0	2	1	1	2	0
Prepackaged syringes									x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Only medication for grandparents in box									x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Organization/structure	x	x			x	x						**4**	**2**	**2**	2	2	1	3	3	1	2	2	1	3	2	2	2	2
Routine & rituals					x							**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Reward after hospital visit					x							**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Double check		x		x					x	x		**4**	1	3	2	2	2	2	**4**	**0**	1	3	2	2	2	2	2	2
Informing 3[d] parties			x	x	x						x	**4**	1	3	2	2	1	3	3	1	**0**	**4**	1	3	1	3	3	1
Other parents					x				x			**2**	0	2	1	1	0	2	1	1	1	1	0	2	1	1	1	1
Parents have knowledge										x		**1**	0	1	0	1	1	0	1	0	0	1	1	0	1	0	0	1
Internet									x			**1**	0	1	1	0	0	1	1	0	1	0	0	1	1	0	0	1
Divorced = less confusion					x							**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
Good communication ex							x					**1**	0	1	0	1	0	1	0	1	1	0	0	1	0	1	1	0
Call mother on sleepover					x							**1**	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1	0
TOTAL FACILITATORS	**17**	**12**	**10**	**16**	**26**	**16**	**12**	**18**	**15**	**6**	**148**	**38**	**11 0**	**53**	**95**	**31**	**11 6**	**10 9**	**38**	**63**	**84**	**32**	**11 5**	**76**	**71**	**84**	**61**
Median per subgroup											*2*	*0*	*1*	*1*	*1*	*0*	*1*	*1*	*1*	*1*	*1*	*0*	*1*	*1*	*1*	*1*	*1*

[a] Differences in interview facilitators are marked by **red bold numbers** [b] Tx = transplantation

APPENDICES

Appendix 1: Socio-demographic questionnaire

Appendix 2: Interview guide

Appendix 3: Author guidelines 'Pediatric transplantation'

APPENDIX 1: SOCIO-DEMOGRAPHIC QUESTIONNAIRE

Name and surname:

- Mother: ……
- Father: ……..

Year of birth:

- Mother: ……
- Father: ……..

Working status:

- Mother: ……
- Father: ……..

Marital status:

- Married
- Divorced
- Living together
- Widow/widower
- Other: ……

Family composition:

- Number of children: ……
- Partners / other involved persons: ……

Name and surname child: ……

Year of birth child: ……

Child's gender:

- Boy
- Girl

Child's age at time of transplantation: ……..

Type of transplantation:

- Kidney transplantation (cross out which is false)
    - Living donor / cadaveric donor
    - 1 kidney / 2 kidneys
- Liver transplantation (cross out which is false)
    - Living donor / cadaveric donor
    - Whole liver / part liver

Pre-transplantation diagnosis: ……..

APPENDIX 2: INTERVIEW GUIDE

Goal

The research goal is to gain more insight in factors which have a positive and a negative influence on medication (non)adherence after kidney and liver transplantation in children up to 11 years.

Research questions

- What is the prevalence of medication nonadherence to immunosuppressants and co-medication amongst non adolescent pediatric liver and kidney transplant patients?
- Which factors positively or negatively influence regular medication taking?

Introduction

First, I will introduce myself: my name is Anouck Claes and I'm a student in the Master of Science in Nursing and Obstetrics at the Katholieke Universiteit Leuven. In the context of this education, I'm conducting a Master's thesis. I have chosen to research medication use after kidney and liver transplantation in children. In essence, I'm going to interview parents of children up to 11 years who have had such a transplantation. Within this interview, I'm going to try to gain more information about your experience with administering medication within your family and which factors may stimulate or hinder the child's medication intake. The goal is therefore to collect information about positive as well as negative factors which may influence medication intake. Literature shows that children often experience difficulty with the correct intake of medication. It's a great challenge, for children as well as their parents to take medication on multiple moments every day. Few literature to date however researches these factors. With the information gained from this research, we will learn more about elements which make medication management harder or easier. Through this, we can eventually develop adequate interventions to better help future patients.

The process will take up about an hour and a half in total. Firstly, an interview is performed. There are no right or wrong answers to the questions I will ask. The aim is to answer the questions as broadly as possible. Anything which in your opinion relates to the subject, your feelings, your thoughts, may be cited. The conversation will be recorded with the aid of a Dictaphone to simplify processing afterwards. I'm the only person who will hear these tapes, which will be destroyed after I have written them out and analyzed them. The data will be completely anonymous and all information gained through this interview will be treated completely confidentially. Do you give permission to record this conversation? I would also like to point out that you have the right not to answer the questions or to end the interview prematurely without having to give an explanation.

Following the interview, a brief questionnaire will be carried out which focuses on possible hurdles concerning medication intake. It consists of 28 questions, where you'll have to indicate in which extent the items is applicable.

Do you have any further questions or are there any unclarities?
Before starting the interview, I would like to ask you to sign the written informed consent form and to fill out a short socio-demographic questionnaire (see appendix 1).

Questions

Key questions

- Could you describe which medication your child has to take in the context of his or her transplantation?
    - Which immunosuppressants does your child take? Immunosuppressants are medications that prevent rejection.
    - In which way is the medication taken (button, orally, ..)
    - Which other medications does your child take?
- Who is responsible for the medication intake at home?
    - Does one parent assume the majority of the responsibility or is it shared equally?
    - Does the child share responsibility?
    - In which way does he or she help?
- Can you describe a typical day in the context of medication administration?
    - What dosage has to be taken and how many times a day?
    - How have you chosen to plan the medication in your daily routine?
    - Are there certain rituals?
- Which factors complicate correct medication intake?
    - Factors regarding the medication intake?

      F.e. taste, smell, form, way of administration, side effects, …
    - Factors regarding the medication regimen?

      F.e. timing, number of administration moments, amount of medication/multiple medications, unclarities regarding the medication or its intake, …
    - Factors regarding the illness?

      F.e. feeling ill, …
    - Factors regarding the child?

      F.e. forgetfulness, refusal, being angry, influence of social aspects (not being able to participate in sports, …), …
    - Factors regarding the parents/family/living situation?

      F.e. divorced parents, other ill family members, forgetfulness, not having refills on time, …

  - Which factor is predominant?
  - Is there a difference between early post-transplant and present?
- Which factors facilitate correct medication intake?
  - Are there certain things that help you?

    F.e. a reward, a certain ritual/structure, distraction, …
  - Have you done these things intentionally or did they become apparent over time?
  - Which factor is most helpful?
  - Is there a difference between early post transplant and present?
- Do you use aids (tricks, systems) to optimize medication intake?
  - At home?

    F.e. an alarm, a medication box, a calendar, …
  - External help?

    F.e. grandparents, friends, other family members, …
- Are there other family members with a chronic illness?
  - If yes, does this have an influence? If yes, in what way?
  - Is medication intake easier with one child in comparison to the other? Why do you think this is? Are the hurdles the same in both children?
- How do siblings react to the fact that their brother or sister has to take medication?

<u>Exploring questions</u>

- Go on….
- So if I understand it correctly… Is this correct?
- How do you mean?
- When was this?
- Can you tell a little bit more about that?
- Can you give an example of what you mean?
- Can you describe what you mean?
- What did you feel at the time?

<u>Concluding questions</u>

- Of everything discussed in this interview, what do you find most important?
- Do you feel like something hasn't been addressed?
- Do you wish to add something that may prove relevant within this research?
- Thank you very much for your participation.

APPENDIX 3: AUTHOR GUIDELINES 'PEDIATRIC TRANSPLANTATION'

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"Organ-Perfusion Support"

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