End-stage renal disease in children: management, outcomes, improvement of care
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GENERAL DISCUSSION
The main objective of this thesis is to evaluate the current quality of care (QoC) for children with end-stage renal disease (ESRD) in the Netherlands and Belgium and to present a new approach for improvement of this QoC for children with ESRD. The Institute of Medicine defines **quality of health care** as ‘the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and to which they are consistent with current professional knowledge’.

In line with this definition we have used a stepwise approach to reach our goal. As a first step, we reviewed the volume, validity and relevance of the existing international guidelines for paediatric chronic renal replacement therapy (cRRT) and of the most frequently used diagnostic tool for establishing vascular disease in ESRD patients, the Pulse Wave Velocity (PWV).

Second, we analyzed the current treatment policies of all Dutch and Belgian centres for cRRT and compared these with the international guidelines’ recommendations and with the actually delivered care in these centres. Patients’ health outcomes are part of these analyses. We focused at one specific area of treatment variation: care for children of parents of non-Western background (immigrants).

Finally, we describe the first results of the RICH-Q project (Renal Insufficiency in Children- Quality assessment and improvement), an initiative which aims to improve QoC by close and structured collaboration of all Dutch and Belgian centres for paediatric cRRT.

In this chapter we will discuss the consequences of the most important results for clinical practice and present recommendations for the research agenda. The main results of the work presented in this thesis are summarized in the panel.

### MAIN RESULTS OF THE THESIS.

1. Existing guidelines for cRRT in children are almost exclusively based on expert opinion or consensus, while evidence is lacking.
2. Current devices that measure Pulse Wave Velocity are unreliable tools in the clinical evaluation of vascular disease in children with end-stage renal disease.
3. Treatment policies in the Dutch and Belgian centres for cRRT in children show important differences which may have impact on treatment outcomes in these children.
4. Children with ESRD of parents of non-Western background, treated in the Netherlands or Belgium, receive a different treatment and have less favourable health outcomes than children of native parents. The reason for these differences in treatment and outcome is unclear.

**Consequences**

Our observations imply that, given the same clinical condition, management depends on in which centre a child with ESRD is treated, e.g. at what estimated Glomerular Filtration Rate cRRT is initiated, what cRRT treatment modality is given to the patient, and how strict
the lifestyle recommendations are. It means that optimal and suboptimal management strategies may be applied in children with otherwise similar conditions and clinical problems. This is remarkable in two highly organized countries with a highly qualified medical care system, and may jeopardize health outcomes for these children. If these disparities exist in these two countries, they may also exist in other European countries and around the world. Suboptimal management strategies may well deteriorate the course of disease as well as the quality of life in these children. Obviously, many of the differences in patient care that we found, such as the significant differences in choice of dialysis modality and lifestyle recommendations, have various different important psychosocial implications for patient and caretakers. To what extent these differences also affect patient outcomes is more difficult to assess as empirical research relating management choices to health outcomes in this field is scarce, demonstrated by our finding that over 95% of the existing guidelines for paediatric cRRT are opinion derived and not based on clinical evidence. The lack of a solid scientific ground for the existing guidelines may also be an explanation for the remarkable deviations of the local policies from the recommendations as stated in these guidelines, and also for the deviations in daily practice in most units from their own stated treatment policies that we found.

We focused at one specific area of treatment variation: care for children of parents of non-Western background (immigrants). The policy of all participating centres in our study is to advocate (pre-emptive) Living Donation (LD) transplantation (Tx) as most advantageous to all patients. Patients from non-western immigrant parents received less often these most favourable modes of renal transplantation, i.e. pre-emptive and LD transplantation than native children. This relatively low number of LD transplantations in immigrants is most likely due to a reluctance of non-Western immigrant parents to donate as compared to native parents. A cultural barrier, different beliefs and attitudes towards donation, but also misunderstandings and miscommunication between patient or caretakers and physician may play a role. We also found that immigrant children had more chance for undergoing an acute rejection, independent from the mode of transplantation. This may also be related to cultural factors and language difficulties, a different awareness of living with a chronic disease or simple misunderstandings between patient and doctor resulting in on average less adherence to the therapy, and, consequently, more rejections. However, in our study most rejections occurred shortly after transplantation during a period of regular hospital visits according to a protocol, and, although we had no reliable tools to measure patient compliance, the occurrence of rejections so soon after transplantation makes non-compliance as an important cause of acute rejection less likely. Instead, biological factors may play a role. Yet, we found no differences in primary disease between immigrant and native children. If transplanted with a kidney from a Deceased Donor (DD), immigrants had significantly more HLA mismatches on the Dr locus, but this did not influence the lower rejection free survival in immigrants. Whether other genetically determined, pharmacokinetic or immunological differences might have influenced the higher rejection frequency in immigrant children remains to be elucidated.

Remarkably, immigrant children received more often hemodialysis (HD) as first mode of cRRT instead of peritoneal dialysis (PD) compared to native Dutch and Belgian children, and spend a longer time on dialysis prior to transplantation. The two major adverse
outcomes found in our study on immigrant patients on dialysis, i.e. the relatively high peritonitis and renal osteodystrophy incidence, share a common important feature with all possible adverse outcomes, which is that prevention of these complications depends heavily on therapy adherence and a disciplined lifestyle of the patient.

Data on measurement validity and reproducibility of devices to measure PWV in adults and children are poorly reported. As a matter of fact, adequate validation studies are often lacking or have not been performed to the modern standards. The results of our two reproducibility studies on devices to measure PWV both indicate that these devices cannot be seen as reliable tools for use in clinical practice in the evaluation of vascular disease in children with ESRD. We found that measurement errors are often larger than the expected ‘real change’ in PWV over time, with the consequence that ‘real change’ in PWV cannot be distinguished from measurement error. Because the reproducibility is insufficient, the measurement technique is not suitable to monitor PWV changes over time in individual children with ESRD. This does not mean that the measurement of PWV is unsuitable for use in clinical studies as it can still be used for longitudinal or comparative studies including sufficiently large groups of patients. The most important conclusion of our study remains that more attention should be paid to proper validation of devices and reproducibility studies.

**Implications for clinical practice**

» **Work within focus groups to enhance quality of care.** Close national and international collaboration between treatment units for paediatric cRRT on a continuous basis with structured and continued peer discussions on treatment protocols and evaluation of patient outcomes is necessary to lay the foundations for progress in this field. First, care could be brought to the next level by sharing insights and protocols. Contrary to the situation in adults, ESRD in children is a rare but serious and life-threatening disorder with a high overall mortality and morbidity. There are about 30 new patients aged < 19 years with ESRD per year in the Netherlands and 20 in Belgium. Patients are cared for in one of 10 small dialysis centres, of which there are 4 in the Netherlands and 6 in Belgium. Concentration of care to 1 or 2 centres per country introduces the problem of long daily travelling for chronic dialysis patients and is therefore not an attractive option. The only solution to improve the QoC in these patients is a close and structured collaboration between these units. In RICH-Q a group of clinicians who work in separate centres with very small numbers of seriously ill patients now collaborate on a continuous basis to improve the QoC in the virtual absence of population-specific evidence. This cooperative way of working increases the shared professional experience, promotes exchanges of experiences and offers at the same time an opportunity to generate more evidence for the management of rare diseases by increasing the number of study objects. Recently, a German centre has joined the RICH-Q group. Evaluation of the project over the next years will show whether this method indeed has lead to a more harmonized treatment of cRRT in children with a better outcome.

» **Increase the number of pre-emptive Tx** in all centres for cRRT in the Netherlands and Belgium. Despite the fact that all centres for cRRT in the Netherlands and Belgium
stated that pre-emptive Tx is the preferred modality of RRT when RRT needs to be initiated, this was realized in only 23% of patients.

- **Foster a system for national validation and local implementation of new knowledge.** Current guidelines need to be adjusted in time and on time, another avenue of national and international collaboration. Example: While current guidelines for topical mupirocin prophylaxis to prevent exit site infections and peritonitis in paediatric cRRT are contradictory, recently large studies showed the preventive effect of local mupirocin prophylaxis and therefore the prophylactic use of mupirocin on the exit site needs to be implemented in clinical practice. As guidelines that are available for management of chronic dialysis in children are not based on empirical research evidence, and quality indicators or benchmarks are lacking, this is a first priority.

- **Make new clinical practice guidelines more effective.** The development process, the validity and importance of the recommendation for practice, and the potential problems and barriers for implementation in clinical practice should be described. Such guidelines should be published in international literature and become available to all paediatric nephrologists and associated disciplines in the world.

**Recommendations for future research**

1. **Identify areas for improvement of QoC, set research priorities.** To improve the QoC for patients with rare diseases such as paediatric ESRD, with the virtual absence of population-specific evidence, novel collaborative approaches are urgently needed. First, out of the many issues open for empirical studies, a **priority list for the current research agenda** need to be developed. Collaborative projects such as RICH-Q offer an opportunity to set research priorities, decide on the utility of adult evidence and foster implementation of treatment guidelines that contain a mixture of consensus based and evidence based recommendations. With such an agenda, the collaboration of treatment centres in designing, conducting, reporting, and implementing study results will be instrumental. From the results of the studies presented in this thesis, priority topics for further research concerning the improvement of QoC for children with ESRD are:

- With respect to **PD catheter care**, long term follow up studies generating data on PD catheter care and health outcomes, i.e. peritonitis incidence and PD catheter survival, will show whether it is useful and cost-effective to strive for stricter guideline adherence or whether the existing recommendations need adjustment.

- With respect to **HD frequency prescriptions**, the association of dialysis frequency and important health outcomes such as quality of life and survival needs to be studied in observational studies and probably experimental designs as well.

- **Reasons for adverse outcomes in non-western immigrants** have to be explored. Potential biological (genetic profile, pharmacokinetics) as well as social and cultural aspects have to be investigated.

- The impact of **treatment modality switches** on short term and longitudinal assessment of HRQoL (as included in the design of the RICH-Q study) should be studied in prospective cohort studies.
2. Reduce cardiovascular disease in children with ESRD. As discussed in Chapters 3, 4 and 5, cardiovascular disease is the most important cause of death in patients with paediatric cRRT. Left Ventricular Hypertrophy (LVH) assessment by heart ultrasound and PWV are frequently used tools to assess cardiovascular disease in studies on children with ESRD. However, our data show that PWV has far more drawbacks than is generally believed. In fact PWV is too unreliable to be used for detecting vascular disease in a clinical setting in children with ESRD. At the same time, another current RICH-Q study found that no data exist on the validity of LVH assessment in children with ESRD by heart ultrasound.

From the results of the studies presented in this thesis, priority topics for further research concerning the assessments methods for cardiac disease are:

» If new device are developed to measure PWV adequate validation studies must be performed and clearly reported before the devices can be used for research or clinical purposes.

» PWV reproducibility studies. These need to include a clear report of the methods of the reproducibility study, the number of observers, the number of measurements and the time period between the measurement, the number of studied individuals and a description of the study population, etc. (as described in detail in chapter 3)

» Heart ultrasound validation studies. The currently used methodology in heart ultrasound and new adjustments to this technique, like Tissue Doppler Investigation, need to be validated for children with ESRD.

REFERENCES