End-stage renal disease in children: management, outcomes, improvement of care
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LESSONS LEARNED FROM EFFORTS TO IMPROVE THE QUALITY OF CARE IN CHILDREN WITH END-STAGE RENAL DISEASE IN THE NETHERLANDS AND BELGIUM

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Quality improvement research strives to bridge the gap between ideal and actual care. Many pediatric diseases are rare, and thus there is by far insufficient evidence to define ‘ideal care’. Low prevalences and generally small patient numbers in centers in which children with rare diseases are treated create considerable barriers for clinical studies and for the development of evidence based guidelines. As a consequence, most existing guidelines are derived from studies in adults and lack any pediatric evidence. Here we focus on pediatric end stage renal disease (ESRD) as an example of a clinical field in which these challenges are encountered.

Contrary to the situation in adults, ESRD in children is a rare disorder: in the western world, the yearly incidence rate of ESRD in patients < 19 years of age is about 6-8 per million age related population. On a population of 3.9 million people < the age of 20 years in the Netherlands and 2.5 million in Belgium, this implies on average about 30 new patients per year in the Netherlands and 20 in Belgium. In order to maintain acceptable travel distances to the dialysis center, patients can choose between several, consequently all very small dialysis centers, of which there are 4 in the Netherlands and 6 in Belgium. ESRD in children is a serious and life-threatening disorder. Data on long term outcomes show that overall mortality in young adults is about 30 times increased. The risk for cardiovascular death in these patients is increased more than 100 times. In survivors, juvenile ESRD has an important impact on somatic and psychosocial functioning in adult life: over 40% of the adult survivors of ESRD in children suffer daily from somatic comorbidity and about 20% are severely disabled. As compared to the general population, these patients are significantly lower educated, more dependent in daily functioning and twice as often unemployed. Despite all progress that has been made in the quality of chronic renal replacement therapy (cRRT), recent data on children on cRRT suggest that most of the long term outcomes may still be applicable to the current population. Until the start of the RICH-Q project (Renal Insufficiency in Children - Quality assessment and improvement), no structural collaboration existed between these centers and there was no consensus on general guidelines with respect to dialysis treatment.

These days, also in pediatric nephrology, registries are emerging, mainly with the aim to provide a platform for observational studies and outcomes research. However, most ESRD registries are limited to only one type of cRRT modality such as (peritoneal) dialysis or transplantation. As far as we know, none of the existing registries in the pediatric ESRD field serve as a basis for network collaboration with regular data comparison, peer discussions and quality improvement. This concept has proven to be successful in other international pediatric networks that strive for quality improvement, e.g. in neonatology, inflammatory bowel disease and cardiology.

RICH-Q started in 2007 as a collaborative project of all Dutch and Belgian pediatric dialysis and renal transplantation centers with the aim to improve the Quality of Care (QoC) for children with ESRD. The aim, methods and early results of the RICH-Q project are presented here as an example of a Quality Improvement (QI) project in a rare disease.
METHODS

Initiation RICH-Q study

After the RICH-Q study was discussed with all Dutch and Belgian pediatric nephrologists, and they agreed to work together, the Dutch Kidney Foundation provided financial support covering the main costs of the project’s organization. In October 2007, the project started with the participation of all 4 Dutch and 5 Belgian centers for pediatric cRRT. In 2009, a new Belgian center started cRRT in children and joined the RICH-Q group. Ethical approval was given by the ethical boards of all participating hospitals and written informed consent was received from all participants and their parents on the required issues. Panel 1 lists the guiding principles on which the RICH-Q project is based.

RICH-Q database

All pediatric patients on chronic dialysis and all patients aged <19 years who were transplanted pre-emptively from October 2007 onwards, are eligible for inclusion in the RICH-Q registry. In an online database, developed and maintained according to the standards of Good Clinical Practice, anonymized data on therapy characteristics and outcomes are registered. The RICH-Q database is comprehensive; details of the treatment, e.g. dialysis schedule, medication and outcome parameters, e.g. calcium- and phosphate levels, left ventricle hypertrophy, etcetera are registered. Continuous data collection is performed by local staff members of the 10 treatment centers, after an extensive training by an experienced research nurse. Online data extraction forms, built with SPSS Dimensions software, are filled in for each included patient four times per year. Part of the research budget is used to reward data collection by financial compensation, to foster continuous data acquisition. An independent research institute (Hans Mak Institute, Naarden, the Netherlands) regularly checks these data for missing values and deviations. Further data monitoring is performed by independent research nurses of this research institute, who check a random sample of 20% of all completed data extraction forms with the local data from patient records. Health related quality of life and psychosocial well-being of the participating children is assessed by validated instruments and parent and child questionnaires twice a year.

Panel 1. RICH-Q Guiding principles

» Collaboration takes place in an open, interactive, non-competitive atmosphere
» Centers have access to overall data from the Good Clinical Practice database on treatment characteristics and health outcomes in which all dialysis and renal transplanted patients of the participating centers are included
» Centers share all data on policy and outcomes with each other
» Working groups with representatives of all centres will define quality indicators based on the latest available evidence
» Data are available to all participants who aim to start an add-on study.
» No center will be forced to change its policy by the RICH-Q group.
Treatment policies
At onset of the study, current local treatment policies were surveyed by an in depth questionnaire. This questionnaire was developed with input from all participating pediatric nephrologists to ensure content validity. It includes questions on the management of hemodialysis (HD), peritoneal dialysis (PD), transplantation (Tx) and the initiation of cRRT.

Feedback and RICH-Q meetings
Since June 2009 all participating centers have on-line access to fortnightly updated information on specific variables for their own center in comparison with the mean of that particular variable of all participating centers, e.g. percentages of patients within normal values, above the upper and below the lower limits for serum calcium and phosphate levels, number of peritonitis in patients with PD. Twice a year all participants meet in “advisory board meetings”. The following topics are among those addressed in these meetings: 1. Differences between treatment policies in the centers, 2. Current status of targets for selected quality indicators, e.g. serum calcium and phosphate, blood pressure, 3. Establishment of a priority list of potential quality indicators 4. Composition of special working groups on specific topics, e.g. cardiovascular disease, peritoneal dialysis adequacy, nutrition and growth, transplantation. The latest available research evidence from the literature on important outcomes from the priority list is discussed. For each outcome it is

Table 1. Number of patients registered in the RICH-Q project on August 1, 2010 by treatment modality at the time of inclusion.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Patients treated with cRRT at start RICH-Q</th>
<th>New cRRT patients since June 2008</th>
<th>Total number of registered patients per centre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD</td>
<td>PD</td>
<td>HD</td>
</tr>
<tr>
<td>NL-1</td>
<td>3</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>NL-2</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>NL-3</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>NL-4</td>
<td>14</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>TotalNL</td>
<td>34</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>B-1</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>B-2</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>B-3</td>
<td>7</td>
<td>5</td>
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<td>B-4</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
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<td>5</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TotalB</td>
<td>20</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>RICH-Q Total</td>
<td>54</td>
<td>57</td>
<td>21</td>
</tr>
</tbody>
</table>

cRRT = chronic Renal Replacement Therapy, HD = hemodialysis, PD = peritoneal dialysis, Tx = transplantation, NL = the Netherlands, B = Belgium, *Only pre-emptive transplantations are included; prevalent patients who had been transplanted before October 2007 were not included.
decided by consensus whether this outcome should serve as a quality indicator or whether more (literature) research is necessary.

The RICH-Q database

On August 1st 2010, 200 patients on cRRT had been included; 135 in the Netherlands and 65 in Belgium (Table 1). Treatment modality at inclusion in the registration was PD in 92 patients, HD in 75 patients and transplantation in 33 patients. The first Renal Replacement Therapy (RRT) modality ever was PD in 91 patients (45%), HD in 77 (39%) and pre-emptive transplantation in 32 patients (16%). Median [range] age at onset was 10.5 [0-18] years, median [range] duration of RRT at start of the study 4.5 [0-209] months.

Activities

Since the start of RICH-Q in 2007, 7 meetings have been held with all participating centers. An overview of on-going projects is given in Table 2. There are three main aims, which are closely related, i.e. 1) harmonization of practices, including selection of guidelines, definition of benchmarks, feedback and comparison of data from all centers, 2) early detection of cardiovascular disease, which is the most important negative outcome, and 3) creating a framework for additional studies. There have been open discussions on the differences in certain outcomes between the centers in relation to treatment policies, definitions of clinical variables and patient characteristics. Working groups have been formed who perform systematic literature reviews to summarize the existing evidence for discussion at the advisory board meetings. Systematic reviews and empirical studies are performed concerning the validity and reliability of cardiovascular surrogate outcome measures in this population.

Examples of important first results of the project

Example 1. Differences in treatment policies. Treatment policies varied between the nine centers participating in the survey in October 2007. Differences were found in several domains, such as the indication for the start of renal replacement therapy, offering of home hemodialysis instead of center dialysis and of the preferred first mode of RRT. As another example, there appeared to be considerable differences in policies with regard to transplantation policy. The minimum accepted donor age varied from 1-5 (median 3) years; the maximum accepted donor age varied from 45 to 60 (median 55) years. Some centers accept non-heart beating donors and some (sometimes other) accept non-related living donors, others do not. Although there is no consensus yet on which policies all centers should adopt, discoveries like these are revelations to the clinicians. In Table 3 some of the policy differences, as well as the actual performed therapies are presented. There is now agreement to strive for common, optimal policies.

Example 2. Comparison of guidelines. For the clinical interpretation of calcium and phosphate levels, the participating pediatric nephrologists reported two different guidelines on which they based their clinical decisions, i.e. normal values from the European Society of Pediatric Nephrology and KDOQI guidelines (Kidney Disease Outcome Quality Initiative). Calcium and phosphate levels from the baseline records of all
dialysis patients in the RICH-Q cohort were compared to the recommended values in both guidelines (Figure 1). This analysis revealed that comparison of clinical data to either one of the guidelines can lead to considerable differences in interpretation, with consequences for treatment decisions. The fact that there is hardly any evidence underlying these guidelines makes it challenging to decide what is ‘optimal care’.

### Table 2. RICH-Q subprojects.

<table>
<thead>
<tr>
<th>Aim</th>
<th>Project</th>
<th>Process</th>
<th>Result and Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmonization of management policies</td>
<td>Comparison of treatment policies</td>
<td>Survey treatment policies in all centers at baseline</td>
<td>Information on unwanted variation in treatment policies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison with existing guidelines</td>
<td>Assessment of the gap between actual care and guidelines</td>
</tr>
<tr>
<td>Identification and prioritisation of</td>
<td></td>
<td>Systematic review</td>
<td>Implementation of guidelines</td>
</tr>
<tr>
<td>guidelines and setting of benchmarks</td>
<td></td>
<td>Consensus procedure on which guidelines to implement</td>
<td>Assessment of the gap between actual care and guidelines and benchmarks</td>
</tr>
<tr>
<td>Feedback of clinical data compared to</td>
<td></td>
<td>6-monthly meetings of pediatric nephrologists</td>
<td>Insight in clinical data</td>
</tr>
<tr>
<td>data from other centers</td>
<td></td>
<td>In depth review of clinical data</td>
<td>Insight in variation between centers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consensus on best practice</td>
</tr>
<tr>
<td>Early detection of cardiovascular</td>
<td>Identification of relevant and valid</td>
<td>SR on validity of Pulse Wave Velocity (PWV) measurement instruments</td>
<td>Information on optimal measurement instrument for PWV</td>
</tr>
<tr>
<td>disease</td>
<td>outcome measures</td>
<td>Reproducibility study PWV</td>
<td>Improved standards for assessing heart ultrasound</td>
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<tr>
<td></td>
<td></td>
<td>Reproducibility study heart ultrasound to detect Left Ventricle Hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Creating a framework for studies</td>
<td>Assembling information on patients from all centers</td>
<td>Good Clinical Practice database Quality of Life questionnaires Add-on studies, e.g. Body Composition Monitor</td>
<td>Extended prospective data available for analysis with increased statistical power</td>
</tr>
</tbody>
</table>

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*Table 2. RICH-Q subprojects.*

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Figure 1. Proportions of the RICH-Q study population (n = 150 dialysis patients) with serum calcium (A) and phosphate (B) levels above and below the standards set by the KDOQI and ESPN guidelines.
DISCUSSION

This article gives an example of the start and early results of a collaborative QI approach in a rare disease, i.e. pediatric ESRD. The RICH-Q project is an example of a group of clinicians working in separate centers with very small numbers of seriously ill patients who now collaborate to improve the quality of care in the virtual absence of population-specific evidence. The generation of evidence for the management of rare diseases is hampered by extremely small sample sizes. Due to the small numbers of patients in small centers it is often not possible to investigate treatment efficacy in an experimental setting.

In the current absence of pediatric-specific evidence, pediatric nephrologists have to assess whether the evidence generated in adults with ESRD is generalizable to children. This is a complex process, which needs to be reassessed and updated regularly. 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.

This multicenter QI project started by identifying unwanted variation in treatment policies across the 9 centers at onset of the study, and currently 10 hospitals providing cRRT in the Netherlands and Belgium. Further regular feedback of information and focus group discussion is expected to lead to more uniformity in clinical policies. Also, in the 6 monthly Advisory Board meetings consensus on the choice of quality indicators is achieved. These quality indicators, or benchmarks, will be used to assess the QoC at the onset of the project by evaluation of benchmark adherence of the clinical data from the patient registry. QoC at study onset will be compared with the results after 3 years of RICH-Q’s process of feedback and peer reviewing to measure QoC change.

In conclusion, this paper provides an overview of the first results of a promising initiative in which collaborative efforts provide an opportunity of QI for the benefit of children with a rare disease, in this case ESRD in the absence of population-specific evidence.

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REFERENCE LIST


