What happens to a child with renal failure

Francesco Emma

Division of Nephrology and Dialysis

Bambino Gesù Children’s Hospital, IRCCS - Rome, Italy
Contribution of pediatric patients to the adult ESKD/transplant population

Fig. 1. Number Pmarp (per million persons reaching the age of 18 years) of young adults who started RRT during childhood reaching the age of 18 years (between 1985 and 2005), by age group at the start of RRT.

32 years old in 2020
40 years old in 2020
The past (and present) of kidney transplantation

40 years old in 2020 (if transplanted at age 10 years)

Adapted from Zand M., Semin Dial 2005
Life expectancy and causes of death in patients with CKD (Canada)
Natural history and cardiovascular risk of a child with ESKD
What is the life expectancy of a child with ESKD?
Late Effects of Renal Insufficiency in Children (LERIC)

- **1972-1992:** all Dutch patients with onset of ESRD <15y
  - 249 patients

- **1999-2000:** survivors aged 20-40
  - 63 had died (25%)

- **2010:** survivors aged 30-50
  - 97 had died (39%)

Mortality rates > 30 x
ANZDATA: long-term follow-up of children with ESKD

Approximately 80% of transplanted children

Less than 50% of children on dialysis
Transplantation is a better treatment at all ages

Expected remaining lifetimes (years) of dialysis and transplant patients according to age

Mortality rates 10 years after the first transplant

USRDS 2005 annual report and OPTN/SRTR 2006 annual report

Adapted from Foster et al, Am J Transpl 2011
Patient survival (2000’s-2010’s)

Kidney Transplantation in Children
Vikas R. Dharnidharka, M.D., M.P.H., Paolo Fiorina, M.D., Ph.D., and William E. Harmon, M.D.

Timing and Outcome of Renal Replacement Therapy in Patients with Congenital Malformations of the Kidney and Urinary Tract
Elke Wühl, Karlijn J. van Stelten, Enrico Venrini, Anna Bjørne, Christoph Wanner, James Goya Head, Oscar Zuriaga, Andres Hovatta, Patrick Niaudet, Runolfur Falsson, Pietro Ravani, Kitty J. Jager, and Franz Schaefer

Wühl et al, Clin JASN 2013
Causes of death in children and in children with ESKD

General population 1–24 years:
- Accidents (38%)
- Homicides (14%)
- Suicides (12%)
- Cancer (7%)
- Cardiac (3%)
- All other (26%)

Hemodialysis 0–19 years:
- Cardiac (32%)
- Infections (11%)
- Withdrawal (5%)
- Malignancy (3%)
- Hyperkalemia (2%)
- All other (47%)

Peritoneal dialysis 0–19 years:
- Cardiac (28%)
- Infections (15%)
- Malignancy (12%)
- Hyperkalemia (2%)
- Other hemorrhages (2%)
- All other (48%)

Transplant 0–19 years:
- Infections (25%)
- Cardiac (22%)
- Malignancy (8%)
- Hyperkalemia (2.7%)
- Other hemorrhages (2.7%)
- All other (39.6%)

Mitsnefes, JASN 2012
How long will the transplant last?
Graft survival according to allograft source and length of follow-up

**Adults + children**

Donor Relationship
First Kidney Transplants 1990-2013

- HLA-Id Sibl  n= 7,048
- 1-Hapl Rel  n= 34,910
- Deceased  n=205,467

**Estimates**

Donor Relationship
First Kidney Transplants 1990-2013

- HLA-Id Sibl  n= 7,048
- 1-Hapl Rel  n= 34,910
- Deceased  n=205,467

Approximately 60%

CTS Collaborative Transplant Study

K-15101-0215
Graft survival in children

Approximately 70%

Wühl et al, Clin JASN 2013

Expected outcome of children transplanted in Rome

Expected patient survival at 30 years: 70-80%

Kidney survival:

After 10 years: ~ 85%

After 20 years: ~ 70%

After 30 years: ~ 30%

Most patients will have or will need another transplant in mid-adulthood
Cardiovascular disease
## CV death

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort</th>
<th>Reference</th>
<th>% CV death</th>
<th>Risk factors, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia / New Zealand</td>
<td>ANZDATA</td>
<td>McDonald et al 2004</td>
<td>45%</td>
<td>Prolonged dialysis</td>
</tr>
<tr>
<td>US</td>
<td>USRDS</td>
<td>Mitsnefes et al 2013</td>
<td>34%</td>
<td>RRT before age of 5 years Improving over time</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>LERIC</td>
<td>Groothoff et al 2002</td>
<td>41%</td>
<td>Long standing dialysis Long standing hypertension</td>
</tr>
<tr>
<td>Germany</td>
<td>University of Heidelberg</td>
<td>Oh et al, 2002</td>
<td>50%</td>
<td>Vascular calcifications</td>
</tr>
<tr>
<td>US</td>
<td>University of Minnesota</td>
<td>Serrano et al 2018</td>
<td>50%</td>
<td>Pre-transplant CVD Graft failure</td>
</tr>
</tbody>
</table>
LERIC cohort follow-up data in 2010

Trend from cardiovascular to non-cardiovascular late mortality in patients with renal replacement therapy since childhood

Judith L. Vogelzang¹,
Karljan J. van Stralen²,
Kitty J. Jager¹
and Jaap W. Groothoff¹

1Department of Paediatric Nephrology, Academic Medical Centre, Emma Children’s Hospital, Amsterdam, the Netherlands
2ERA-EDTA and ESPN/ERA-EDTA Registries, Department of Medical Informatics, Academic Medical Centre, Amsterdam, the Netherlands

LERIC cohort
CKD since childhood
Born before 1979

1st Follow-up
Year 2000
Age 20-40

2nd Follow-up
Year 2010
Age 30-50

Shift from cardiovascular disease to infections as the main cause of death

Changes in medical practice? Patient selection overtime?

Nephrol Dial Transpl 2013
Atherosclerosis timeline

Adapted from Pepine et al. Am J Cardiol 1998
Vascular calcifications

Atherosclerotic calcification is more important in cardiovascular mortality risk
Tunica media calcification is more important in vascular stiffness
Vascular calcifications

Coronary and aortic calcifications in a 27 y/o man with ESKD in childhood

Figure 2. Coronary calcium scores in 24 male and 13 female ESRD patients with childhood-onset CRF. Symbols denote present treatment modality (●, dialysis; ○, after transplantation). The broken and solid lines indicate the 75th, 90th, and 95th reference percentiles of calcium scores.

<table>
<thead>
<tr>
<th></th>
<th>Calcium Score</th>
<th>IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.25</td>
<td>0.45*</td>
</tr>
<tr>
<td>ESRD duration</td>
<td>0.53†</td>
<td>0.32‡</td>
</tr>
<tr>
<td>Cumulative time undergoing dialysis</td>
<td>0.33‡</td>
<td>0.37‡</td>
</tr>
<tr>
<td>Time-integrated mean plasma intact-PTH</td>
<td>0.60§</td>
<td>0.13</td>
</tr>
<tr>
<td>Cumulative serum calcium</td>
<td>0.38‡</td>
<td>0.47*</td>
</tr>
<tr>
<td>Cumulative serum phosphate</td>
<td>0.31</td>
<td>0.40‡</td>
</tr>
<tr>
<td>Cumulative serum calcium-phosphate product</td>
<td>0.36‡</td>
<td>0.50*</td>
</tr>
<tr>
<td>CRP</td>
<td>0.62§</td>
<td>0.03</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>0.35‡</td>
<td>0.18</td>
</tr>
</tbody>
</table>
LERIC cohort: cardio-vascular disease in 2000

(Mean age 29 years; at time investigation: 80% transplant - 20% dialysis)

<table>
<thead>
<tr>
<th></th>
<th>Male patients (N 75)</th>
<th>Female patients (N 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systolic blood pressure</td>
<td>mm Hg 135 (range 81 to 179)</td>
<td>mm Hg 120 (range 65 to 186)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>mm Hg 83 (range 45 to 112)</td>
<td>mm Hg 79 (range 43 to 116)</td>
</tr>
<tr>
<td>Interventricular septal thickness</td>
<td>mm 10.9 (SD 2.4)</td>
<td>mm 9.7 (SD 2.9)</td>
</tr>
<tr>
<td>Posterior wall thickness</td>
<td>mm 10.8 (SD 2.0)</td>
<td>mm 9.3 (SD 1.8)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter</td>
<td>mm 50.7 (SD 6.0)</td>
<td>mm 47.0 (SD 5.2)</td>
</tr>
<tr>
<td>Left ventricular mass</td>
<td>g 257 (SD 91)</td>
<td>g 186 (SD 65)</td>
</tr>
<tr>
<td>Left ventricular mass index</td>
<td>g/m2 150 (SD 45)</td>
<td>g/m2 119 (SD 43)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>number 35</td>
<td>47% 25</td>
</tr>
<tr>
<td>Left ventricular mass/LEFT ventricular volume ratio</td>
<td>g/mL 2.1 (range 1.0 to 3.4)</td>
<td>g/mL 1.8 (range 1.0 to 4.6)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5 (range 0.5 to 3.6)</td>
<td>1.6 (range 0.9 to 3.2)</td>
</tr>
<tr>
<td>E/A ratio _1.0</td>
<td>number 9</td>
<td>-12% 9</td>
</tr>
<tr>
<td>Aortic valve regurgitation</td>
<td>number 17</td>
<td>-23% 15</td>
</tr>
<tr>
<td>Mitral valve regurgitation</td>
<td>number 22</td>
<td>-29% 19</td>
</tr>
<tr>
<td>Shortening fraction</td>
<td>% 39 (range 27 to 61)</td>
<td>39 (range 28 to 85)</td>
</tr>
<tr>
<td>Aortic valve calcifications</td>
<td>number 19</td>
<td>25% 8</td>
</tr>
<tr>
<td>Wall irregularities</td>
<td>number 24</td>
<td>32% 14</td>
</tr>
</tbody>
</table>

Gruppen et al, Kidney Int 2003
Obesity and metabolic syndrome in renal transplanted children

6658 children - 649 obese (10%)

TABLE 3. Causes of Death in Obese Versus Nonobese Children

<table>
<thead>
<tr>
<th></th>
<th>Nonobese, n (%)</th>
<th>Obese, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>98 (28)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>53 (15)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Cancer/malignancy</td>
<td>45 (13)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>24 (7)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>99 (28)</td>
<td>13 (36)</td>
</tr>
</tbody>
</table>
LERIC cohort: comparison 2000-2010

Vogelzang et al, Nephrol Dial Transpl 2013
How are they doing for the rest?
Adult height in patients with advanced CKD requiring RRT during childhood

Growth before and after transplantation is improving (NAPRTCS)

Height and Weight Z scores at the time of kidney transplantation

Height Z scores after kidney transplantation

Bertram et al Nat Rev Nephrol 2016
NAPRTCS 2011 Annual Report
Steroid avoidance, rhGH and less rejections!

Corticosteroid-free kidney transplantation improves growth (TWIST study)

<table>
<thead>
<tr>
<th></th>
<th>CW (n = 53)</th>
<th>CC (n = 53)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHtSDS adjusted for pubertal status and baseline value (SE)</td>
<td>0.57 (0.13)</td>
<td>0.33 (0.14)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Webb et al, Transplantation 2015

Living-donor graft rejection according to transplantation era


rhGH in children with CKD, undergoing dialysis and after renal transplantation

Holmberg and Jalanko, Nat Rev Nephrol 2016
Steroid avoidance also improves cardiovascular status

Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation

Britta Höcker1, Lutz T. Weber1,2, Reinhard Feneberg1, Jens Drube3, Ulrike John4, Henry Fehrenbach5, Martin Pohl5, Miriam Zimmering6, Stefan Fründ3, Günter Klaus5, Elke Wühl1 and Burkhard Tönshoff5

SBP

DBP

BP medications

Metabolic syndrome

Hocker et al, Nephrol Dial Transpl 2010
**LERIC cohort: bone disease in 2000**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone deformities</td>
<td>26%</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>13%</td>
</tr>
<tr>
<td>Aseptic bone necrosis</td>
<td>13%</td>
</tr>
<tr>
<td>Disability</td>
<td></td>
</tr>
<tr>
<td>- mild</td>
<td>11%</td>
</tr>
<tr>
<td>- severe</td>
<td>7%</td>
</tr>
<tr>
<td>- invalidating</td>
<td>18%</td>
</tr>
</tbody>
</table>

*Nowadays, we are probably doing better!*
LERIC cohort: malignancies in 2010

Long-Term Risk of Cancer in Survivors of Pediatric ESRD

Sophie Ploos van Amstel,* Judith L. Vogelzang, Marcus V. Starink, Kitty J. Jager, and Jaap W. Groothoff*

- Median age: 33.5 years
- Median Transplant exposure: 18.4 years
- Malignancies in 21% of patients
  - 80% cutaneous
  - PTLD most prevalent non-skin
- Death secondary to cancer: 12%

HR for squamous cell carcinoma > 800 x after age 40
Causes of ESKD in children

Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA–EDTA registry

Nicholas Chesnaye • Marjolein Bonthuis • Franz Schafer • Jaap W. Groothoff • Enrico Verrina • James G. Heaf • Augustina Jankauskiene • Viktorija Lukosiene • Elena A. Molchanova • Conceicao Mota • Amira Peco-Antić • Ilse-Maria Ratsch • Anna Bjørre • Dimitar L. Roussinov • Alexander Sukalo • Rezan Topaloglu • Koen Van Hoeck • Ilona Zagódzdon • Kitty J. Jager • Karlijn J. Van Stralen • on behalf of theESPN/ERA–EDTA registry

PUV
Prune Belly
Neurogenic bladder
Severe bladder hypoplasia
Other...
Urological problems

DOI 10.1007/s00383-011-2946-9

REVIEW ARTICLE

Posterior urethral valves: long-term outcome

Paolo Caione · Simona Gerocarni Nappo

<table>
<thead>
<tr>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total records</td>
<td>45</td>
</tr>
<tr>
<td>Prenatal diagnosis</td>
<td>8</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
</tr>
<tr>
<td>Patients missed at follow-up</td>
<td>20</td>
</tr>
<tr>
<td>Patients in the study</td>
<td>24</td>
</tr>
<tr>
<td>Age (years)</td>
<td>18–34</td>
</tr>
<tr>
<td>Mean age at follow-up (years)</td>
<td>23</td>
</tr>
<tr>
<td>CRF</td>
<td>13</td>
</tr>
<tr>
<td>ESRD</td>
<td>5</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>3</td>
</tr>
<tr>
<td>Dialysis</td>
<td>2</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td>9</td>
</tr>
<tr>
<td>Normal semen</td>
<td>23</td>
</tr>
<tr>
<td>Azoospermia and epididymitis</td>
<td>1</td>
</tr>
<tr>
<td>Normal sexual activity</td>
<td>21</td>
</tr>
<tr>
<td>Limited or absent sexual activity</td>
<td>9</td>
</tr>
</tbody>
</table>

Dysfunctional voiding
Detrusor overactivity
High urine residue (hypocontractilities)
Clean intermittent catheterization
Fertility

~20% of adults have normal testicular function

Fertility index:
- Control population: 13.0
- Dialysis: 0.2
- Transplant < 2 years: 5.5
- Transplant > 2 years: 9.3

Fertility is restored soon after transplantation
Pregnancy rates < general population (patient choice?)
Preserved graft function if normal baseline GFR

Increased risk of:
- pre-eclampsia
- low birth weight
- prematurity
More difficulties:

- completing education
- achieving high level education
- securing an employment
- developing intimate relationships
Unemployment

Unemployment rate (%)

- Dutch general population
- LERIC dialysis
- LERIC transplant
- Broyer et al transplant

Groothoff et al. J Pediatr 2005
Broyer et al, Transplantation 2004
Dutch National Bureau Statistics
# QoL

## Quality of life: very good mental QOL!

RAND-36 scores of transplanted and dialysis patients

<table>
<thead>
<tr>
<th></th>
<th>LERIC Tx patients (n=107)</th>
<th>Impaired QOL</th>
<th>LERIC Dx patients (n=28)</th>
<th>Impaired QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>22  14-30</td>
<td>No</td>
<td>57  38-75</td>
<td>Yes</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>36  27-45</td>
<td>Yes</td>
<td>61  43-79</td>
<td>Yes</td>
</tr>
<tr>
<td>Role limitations</td>
<td>25  17-33</td>
<td>No</td>
<td>54  32-76</td>
<td>Yes</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health Perceptions</td>
<td>41  32-50</td>
<td>Yes</td>
<td>68  51-85</td>
<td>Yes</td>
</tr>
<tr>
<td>Physical Component Summary</td>
<td>30  21-40</td>
<td>No</td>
<td>64  46-82</td>
<td>Yes</td>
</tr>
<tr>
<td>Role limitations Emotional</td>
<td>17  10-24</td>
<td>No</td>
<td>18  4-32</td>
<td>No</td>
</tr>
<tr>
<td>Mental Health</td>
<td>23  15-31</td>
<td>No</td>
<td>21  6-36</td>
<td>No</td>
</tr>
<tr>
<td>Vitality</td>
<td>34  25-43</td>
<td>No</td>
<td>39  21-57</td>
<td>No</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>23  15-31</td>
<td>No</td>
<td>26  10-42</td>
<td>No</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>23  15-31</td>
<td>No</td>
<td>12  0-24</td>
<td>No</td>
</tr>
</tbody>
</table>

Courtesy J Groothoff
OPBG: QOL in 67 adult pediatric renal transplants (age 23±4)

<table>
<thead>
<tr>
<th>QOL score</th>
<th>N° of items</th>
<th>Mean (max 100)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical well-being</td>
<td>7</td>
<td>72.3</td>
<td>25.6</td>
</tr>
<tr>
<td>Psychological well-being</td>
<td>9</td>
<td>67.8</td>
<td>12.9</td>
</tr>
<tr>
<td>Diet &amp; nutrition</td>
<td>2</td>
<td>85.6</td>
<td>26.0</td>
</tr>
<tr>
<td>Self perception (physical)</td>
<td>4</td>
<td>76.2</td>
<td>25.4</td>
</tr>
<tr>
<td>Social integration</td>
<td>6</td>
<td>48.8</td>
<td>14.3</td>
</tr>
<tr>
<td>Overall score</td>
<td></td>
<td>70.4</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Significantly worse QOL if co-morbidities
Thank you

francesco.emma@opbg.net