Epidemiology of kidney diseases in children

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Definition of Epidemiology

• The patterns, causes, and effects of health and diseases in defined populations

• It informs policy decisions by identifying risk factors for disease and targets for preventive healthcare

• It includes disease aetiology, transmission, outbreak investigation, disease surveillance and screening, monitoring, and comparisons of treatment effects such as in clinical trials
What disease was the top non-communicable cause of global years of life lost, 1990-2013?
What disease was the top non-communicable cause of global years of life lost, 1990-2013?

- CKD
- 3,200,000 die annually as no access to RRT
- We are unlikely to be able to provide RRT to so many people
- To stem the epidemic we need to concentrate on prevention
- However, there is still a big excess mortality even if RRT is offered

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What have we learnt about CKD from epidemiological studies?

• Prenatal influences on renal development
• The effect of the obesity epidemic
• AKI
• Renal replacement therapy
  – Racial and economic disparities
  – Prognosis
  – Complications
Prenatal risk factors for CKD


• A US population-based, case-control study: 1994 patients with childhood CKD and 20,032 controls

• The prevalence of CKD was 126.7 cases per 100,000 births.

• The adjusted ORs for CKD:
  – 2.88 for low birth weight
  – 1.54 for maternal gestational DM
    • Particularly dysplasia
  – 1.24 for maternal overweight
  – 1.26 for maternal obesity
    • Particularly obstructive uropathy
Lower fetal and early infant weight growth is associated with smaller kidney volume at age 6 years


• Examined the associations of longitudinally measured fetal and infant growth with kidney development in school-aged children

• Growth of 6482 children was followed from fetal life

• At age 6 years
  – kidney volume by ultrasound
  – GFR was estimated

• Fetal weight, birth weight, and weight at 6 months were positively associated with childhood kidney volume and GFR
### Birth weight, gestation and neonatal history

<table>
<thead>
<tr>
<th></th>
<th>Infants on dialysis</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>26%</td>
<td>12%</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>Prematurity and small for gestational age</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>HtSDS at birth</td>
<td>-0.42 to -0.69</td>
<td></td>
</tr>
</tbody>
</table>

*Mekhali 2010, Greenbaum 2011, Rees 2011, Laakkonen 2010*
The role of genetics and perinatal factors in CKD

Environment
- IUGR
- Prematurity
- Maternal obesity
- Maternal diabetes
- Medications

Genetics

Low nephron number

Glomerulosclerosis

Albuminuria
- CKD

Glomerular and systemic hypertension

Glomerular hypertension

Can modification of these factors could reduce the risk of childhood CKD?

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Childhood obesity

• Has risen substantially worldwide in less than one generation
• USA: average child weight has risen by more than 5 kg within three decades: a third are overweight or obese
• Some low-income and middle-income countries have reported similar or more rapid rises, despite continuing high levels of undernutrition
Mean Body Mass Index SDS by country

BMI SDS

International Pediatric Peritoneal Dialysis Network
Obesity

- ↑ Insulin resistance
- ↑ Inflammatory cytokines
- ↑ Sympathetic activity
- ↑ Oxidative stress
- ↑ Leptin
- ↓ Adiponectin

↑ BP

CVD

↑ Mortality

↑ RAS

Glomerular hyperfiltration

↑ BP

CKD

↑ Mortality

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AKI at different ages

Moghal, Clin Nephrol 1998

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Incidence of CKD in 126 children with AKI and no preceding renal disease after 1 to 3 years follow up

- High mortality rate in the first 5 years post AKI (up to 20%)
- 10% GFR <60 ml/min/1.73m²
- 47% at risk of CKD
  - GFR 60-90 ml/min/1.73m²
  - GFR >150 ml/min/1.73m²
  - Hypertension
  - Microalbuminuria

L.Rees  Mammen AJKD 2012
Factors that might increase the risk of CKD

- Neonates
- Weight 10th percentile
- Post–cardiac surgery
- Nephrotoxin use
- PRISM III score
- Lowest haemoglobin
- Lowest arterial PO2
- Paediatric ICU / Hospital length of stay
- ECMO
- AKIN stage
- Need for dialysis
Large registries of children with CKD that provide epidemiological data

• National registries
  – CKiD
  – NAPRTCS
• IPDN
• ESPN/EDTA-ERA
What has epidemiology taught us about RRT in children?

- **CAKUT**: 40%
- **Median GFR at start of dialysis**: 8 to 9 ml/min/1.73m²
- **Starting RRT modality in Europe**:
  - PD 47%
  - HD 33%
  - Pre-emptive transplant 20%
What has epidemiology taught us about RRT in children?

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Per million age related population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe overall</td>
<td>5.5</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>3.6</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>8.1</td>
</tr>
<tr>
<td>USA</td>
<td>11.6</td>
</tr>
</tbody>
</table>
Variability throughout the world

264 neonates started chronic dialysis in 32 countries between 2000 and 2011

<table>
<thead>
<tr>
<th>Region</th>
<th>% of under two year olds on dialysis that are neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>18.3%</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>18.1%</td>
</tr>
<tr>
<td>ANZDATA</td>
<td>6.8%</td>
</tr>
<tr>
<td>Japanese Registry</td>
<td>8.6% of &lt; 5 year olds</td>
</tr>
</tbody>
</table>

*ESPN/ERA-EDTA, IPPN, ANZDATA and Japan. KI, 2014*
### Effect of gross national income on numbers of young children taken onto RRT programmes

<table>
<thead>
<tr>
<th>Age at start of dialysis</th>
<th>Gross national income in $000s per capita</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;28</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>19</td>
</tr>
<tr>
<td>1–3 years</td>
<td>11</td>
</tr>
</tbody>
</table>

*IPPN, PDI, 2012*
Proportion of children on RRT by country who have a functioning transplant

Harambat, Ped Nephrol 2014
Non medical factors explain country differences in the rate of transplantation

Harambat, Ped Nephrol 2014

32 countries in Europe with a paediatric RRT program

• Overall 62% had a transplant

• One per million population increase in donation rate from deceased donors was associated with a 5% increase

• A paediatric priority policy increased this by up to x 3

• One per million population increase in living donation rate was associated with a 14% increase

• The percentage of functioning transplants was also strongly associated with the gross domestic product
Effect of ethnic background on transplant survival in the United States

Graft survival (%) vs Years post-transplant.

Race/ethnicity:
- Black
- Hisp
- White

Graft survival table:

<table>
<thead>
<tr>
<th>Graft failure</th>
<th>30 Days</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N at risk</td>
<td>Graft survival, 95% CI</td>
<td>N at risk</td>
<td>Graft survival, 95% CI</td>
<td>N at risk</td>
</tr>
<tr>
<td>Overall</td>
<td>3342</td>
<td>96.6% (96.1–96.9)</td>
<td>2950</td>
<td>95.2% (94.4–95.9)</td>
<td>2480</td>
</tr>
<tr>
<td>White</td>
<td>1358</td>
<td>98.3% (97.5–98.9)</td>
<td>1174</td>
<td>94.5% (93.2–95.7)</td>
<td>993</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1090</td>
<td>98.8% (98.1–99.4)</td>
<td>964</td>
<td>96.2% (95.0–97.3)</td>
<td>826</td>
</tr>
<tr>
<td>Black</td>
<td>894</td>
<td>98.7% (97.8–99.3)</td>
<td>812</td>
<td>94.8% (93.3–96.2)</td>
<td>661</td>
</tr>
</tbody>
</table>
Graft survival:
First paediatric kidney only transplants in the UK, 1975 - 2004

% Graft survival

Years since transplant

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Cadaveric/Living

Cadaveric
living

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Graft survival: First paediatric kidney only transplants in the UK, 1975 - 2004

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Living donation is of particular benefit for the under 2s

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Transplant outcome according to HLA
Graft survival for retransplants 2000-2008 by DR mismatches at first and second transplant

Gralla, Transplantation 2013
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Effect of creatinine at 10 years post transplant on long term outcome

Ellis, NAPRTCS, Pediatr Nephrol 2008

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Initial steroid sensitivity is highly predictive of post-transplant FSGS recurrence


150 transplanted patients with SRNS

- 25 children genetic or familial SRNS and did not experience post-transplant recurrence
- 46% developed post-transplant recurrence
  - 26 of 28 (93%) patients with initial steroid sensitivity
  - 26 of 86 (30%) patients resistant from the outset
A suggested clinical paradigm for idiopathic nephrotic syndrome.

Wen Y. Ding et al. JASN 2014;25:1342-1348
A suggested clinical paradigm for idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is stratified (where possible) according to clinical parameters into “circulating factor disease” and “genetic disease.” This segregates into high and low risk factors for post-transplant disease recurrence.
The growth of our patients is improving:

Growth of children on RRT in 2 eras

- EDTA 1985-88
- HB 1998-2009

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Prevalence of anaemia, IPPN 2012
Elevated serum phosphate increases mortality risk

Adapted from Block, 1998

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Adapted from Block, 1998
Elevated serum phosphate increases mortality risk

The mortality rate increases by 6% for each 0.3mmol/L rise in phosphorus levels

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PTH control in 890 children and adolescents on PD: Centre Variation

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International Pediatric Peritoneal Dialysis Network
% of patients at different PTH ranges with:
• bone pain, fractures, deformities, osteopaenia,
• growth abnormalities
• ectopic calcification
• ↑CaxP

Percentage of patients with complications

<table>
<thead>
<tr>
<th>PTH pg/ml</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>0-100</td>
<td>10</td>
</tr>
<tr>
<td>100-200</td>
<td>20</td>
</tr>
<tr>
<td>200-300</td>
<td>30</td>
</tr>
<tr>
<td>300-500</td>
<td>40</td>
</tr>
<tr>
<td>500-1000</td>
<td>50</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>60</td>
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</table>
Mortality after first transplant (17,468 children)
Percentage survival by age at start of dialysis in 2,867 patients (US, 2008)
Adjusted 5 year survival by age and dialysis modality \textit{(US 2009)}

**Hemodialysis: age 0-9**
- 1993-1997
- 1998-2002

**Peritoneal dialysis**

Survival probability

Months after initiation: 0, 12, 24, 36, 48, 60

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Mortality from CVD on dialysis

Annual mortality (%)

age range, years

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Adapted from Foley, 1998
Benefits of transplantation on life expectancy

- Expected remaining lifetimes in ESRD & transplant patients

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