DETECTION OF CKD IN EARLY STAGES
LONG TERM FOLLOW-UP
FROM CHILDREN TO ADULT AGE

Rosanna Coppo
Turin, Italy
CKD in children

short-term outcome (childhood): dialysis, transplantation

long-term outcome in adult life
30-40% CAKUT: congenital abnormalities of the kidney and urinary tract

10-20% CONGENITAL RENAL DISEASES: tubular, cystic, metabolic diseases, hereditary nephritis

20% acquired glomerular diseases
Renal congenital hypodysplasia
British Association Pediatric Nephrology (BANP) report, Lewis, 2008

- Renal dysplasia with /without VU reflux is the most common cause of ESRF in the childhood population.

- There are overlaps between CAKUT and VUR nephropathy and the distinction is quite arbitrary.

- Joining the two groups, they account for 32% of childhood ESRF
Renal dysplasia/reflux nephropathy

Renal hypodysplasia
Congenital VUR
Obstructive uropathy

renal mass reduction
Hypothesis for the development of pyelonephritic scarring

- Acute pyelonephritis
- High grades of VUR
- Delays in treatment
- Recurrent pyelonephritis
CAKUT progression:
GFR improves from 0 to 3 years of age
is stable between 3 and 11 y;
slowly decreases in 50% of the cases
when baseline GFR is < 40 ml/min/1.73 m².

We expect that several subjects with CAKUT will reach ESRF in adult life.
What do we know about chronic renal failure in young adults? II. Adult outcome of pediatric renal disease

Guy H. Neild
### Causes of ESFR in children in Europe and in USA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Number</th>
<th>Age (years)</th>
<th>A UNKNOWN (%)</th>
<th>B CAKUT (%)</th>
<th>C CONGENITAL (%)</th>
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<td>USRDS (2005)</td>
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<td>UK in Children</td>
<td>UK Renal Registry</td>
<td>USRDS USA Renal Registry</td>
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<td>Reg.</td>
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<tr>
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<tr>
<td>0-15</td>
<td>18-21</td>
<td>22-31</td>
<td>32-39</td>
<td>0-19</td>
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<tr>
<td></td>
<td>397</td>
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<td>2089</td>
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<td></td>
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<td>2521</td>
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<tr>
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<td>1447</td>
<td>2089</td>
<td>1112</td>
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<td></td>
<td>397</td>
<td>1447</td>
<td>2089</td>
<td>1112</td>
<td></td>
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</tr>
<tr>
<td><strong>Dysplasia and/or VUR</strong></td>
<td>32%</td>
<td>14%</td>
<td>10%</td>
<td>8%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>19%</td>
<td>4%</td>
<td>1%</td>
<td></td>
<td></td>
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<tr>
<td><strong>Obstructive nephropath</strong></td>
<td>15%</td>
<td>12%</td>
<td>7%</td>
<td>6%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>12%</td>
<td>1%</td>
<td>1%</td>
<td></td>
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</tr>
<tr>
<td><strong>Tubulo/inter diseases</strong></td>
<td>8%</td>
<td>6%</td>
<td>3%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
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</table>
30-40% CAKUT: congenital abnormalities of the kidney and urinary tract

10-20% CONGENITAL RENAL DISEASES: tubular diseases, nephronophthysis, cystic nephropathy (recessive PKCD), metabolic diseases (primary hyperoxaluria), hereditary nephritis (Alport’s s) and congenital nephrotic syndrome.
<table>
<thead>
<tr>
<th>Renal disease</th>
<th>BAPN children</th>
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</thead>
<tbody>
<tr>
<td>Age y.</td>
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<td>N.cases</td>
<td>913</td>
</tr>
<tr>
<td>Dysplasia and/or VUR</td>
<td>32%</td>
</tr>
<tr>
<td>Obstructive nephropathy</td>
<td>15%</td>
</tr>
<tr>
<td>Tubulo/interstdiseases</td>
<td>8%</td>
</tr>
<tr>
<td>Glomerular diseases</td>
<td>23%</td>
</tr>
<tr>
<td>Congenital NS</td>
<td>5%</td>
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</table>
ITALIAN REGISTRY OF CHILDREN IN CKD TREATED WITH DIALYSIS
mean age 8.7±6 years old

- congenital renal diseases
- acquired renal diseases
<table>
<thead>
<tr>
<th>Glomerular disease so severe to progress to ESRF within childhood</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Age y.</th>
<th>BAPN UK</th>
<th>BAPN UK</th>
<th>NAPRTCS USA</th>
<th>NAPRTCS USA</th>
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<tbody>
<tr>
<td>8-11</td>
<td>27%</td>
<td>26%</td>
<td>8%</td>
<td>19%</td>
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<tr>
<td>12-15</td>
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<td></td>
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<tr>
<td>6-12</td>
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<tr>
<td>13-20</td>
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</table>
### Glomerular disease leading to ESRF in childhood

<table>
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<tr>
<th>Glomerular Disease</th>
<th>Percentage</th>
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<tr>
<td>Age y</td>
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<tr>
<td>IgA nephropathy</td>
<td>1%</td>
</tr>
<tr>
<td>Primary FSGS</td>
<td>10%</td>
</tr>
<tr>
<td>Mesangiocapillary GN</td>
<td>1%</td>
</tr>
<tr>
<td>Alport’s Syndrome</td>
<td>1%</td>
</tr>
<tr>
<td>Systemic lupus erythemathodes</td>
<td>1%</td>
</tr>
<tr>
<td>Henoch-Schoenlein purpura GN</td>
<td>2%</td>
</tr>
<tr>
<td>Unspecified GN</td>
<td>1%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>22% of all causes of ESRF</strong></td>
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<tr>
<td>Glomerular disease</td>
<td>0-15</td>
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<tr>
<td>---------------------------</td>
<td>------</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>1</td>
</tr>
<tr>
<td>Primary FSGS</td>
<td>10</td>
</tr>
<tr>
<td>Mesangiocapillary GN</td>
<td>1</td>
</tr>
<tr>
<td>Alport’s Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Systemic lupus erythemmat.</td>
<td>1</td>
</tr>
<tr>
<td>HS purpura GN</td>
<td>2</td>
</tr>
<tr>
<td>Unspecified GN</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>22</td>
</tr>
<tr>
<td>Age y.</td>
<td>BAPN children</td>
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<tr>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>8-11</td>
<td>27%</td>
</tr>
<tr>
<td>12-15</td>
<td>26%</td>
</tr>
<tr>
<td>18-21</td>
<td>28%</td>
</tr>
</tbody>
</table>

- Glomerular diseases
- Uncertain etiology
In adults in 2007: 28%
Underdiagnosed CAKUT or Glomerular diseases?

UK Pediatric Registry.
In 1976: 39%
In 2008: 3%
CRF without diagnosis in children in UK registries
IgA nephropathy: the commonest glomerulonephritis in the world

In about 25-30% of children by screening in Japan, South Korea, Taiwan

Adults

Children

20%
Patient A: detected by screening : survival 12 years

Patient B: proteinuria : survival 7 years

Patient C: hypertension, reduced GFR: survival 2.5 years

GFR

Geddes et al NDT 2003
IgA Nephropathy in children

- The ERA-EDTA Registry reported that 67% of IgAN patients who enter dialysis are aged between 25 and 55
  (22% < 30 years)

- Since the decline of IgAN is slow
  (25% of the cases need dialysis in 20 years)

It is clear that several progressive IgAN begin in the childhood
Screening program in Japan:
Since 1972 in children
Since 1983 in workers and resident > 40 y.o.

In Japanese population
High prevalence of dialysis and high prevalence of proteinuria

Non diabetic, non hypertensive proteinuric patients.
In Japan 0.9% in USA 0.4%
Clinical manifestation of IgAN

Asymptomatic microscopic hematuria/proteinuria

IgAN

others
IgAN is the most common glomerular disease in the world and has often its origin in childhood

- IgAN in the young: often defected by chance

- In several cases the disease manifests as hypertension with minimal urinary abnormalities or in reduced GFR and no renal biopsy is performed

In Japan in the last decade the frequency of ESFR due to GN changed from 10,000 to 9,000/year due to early screening programme
The late referral to dialysis is dangerous: there is a need to identify the condition of CKD in adult subjects before complete loss of kidney function.

Conditions at risk for CKD must be detected as early as possible to establish a correct management of CKD complications.
Cardiovascular risk is increased in CKD

Increased Arterial Stiffness in Young Adults with End-Stage Renal Disease since Childhood

JAAP W GROOTHOFF, MARIKEN P GRUPPEN, MARTIN OFFRINGA,ERIC DE GROOT, WILLEM STOK, WILLEM JAN BOS, JEAN CLAUDE DAVIN,
Death is far more common than ESRD in CKD patients

27,998 CKD patients followed up for up to 66 months

Keith DS et al. Arch Intern Med 2004; 164: 659-663
Treat the **kidney** to protect your **heart**!

de Zeeuw, 2004

Treating kidney disease means decrease morbility and mortality due to cardiovascolar disease
How early should we start the search for CKD and related factors favouring cardio-vascular disease?

In the pediatric age, several CKD can be unidentified.

Conditions favouring CKD may be operating in life, very early, even prenatally.
PRENATAL CONDITIONING OF RENAL AND CARDIOVASCULAR DISEASE

1965 Rose:
ISCHEMIC CARDIAC DISEASE IN ADULTS WAS ASSOCIATED WITH HIGH MORTALITY RATE IN THE SAME FAMILY
Low Birth Weight Increases Risk for End-Stage Renal Disease

Bjørn Egil Vikse,†‡ Lorentz M. Irgens,†§ Torbjørn Leivestad,‖ Stein Hallan,¶** and Bjarne M. Iversen†‡

Low birth weight increases risk for ESRD


Risk for ESRD increased by 70% when birth weight <2,500 g

The association remains significant even after adjustment for congenital malformations, multiple births, maternal age, maternal pre-eclampsia.
The risk does not involve hereditary or congenital renal diseases only, but also acquired glomerular diseases.

Table 4. RR for different causes of ESRD according to birth weight: Births 1967 to 2004, ESRD 1980 to 2005, Norway

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Glomerular Disease</th>
<th>Interstitial Nephritis</th>
<th>Congenital or Inherited Causes</th>
<th>Diabetes</th>
<th>Other Causes</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>RR</td>
<td>P</td>
<td>n</td>
<td>RR</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>32</td>
<td>1.5 (1.03 to 2.2)</td>
<td>0.04</td>
<td>7</td>
<td>1.6 (0.70 to 3.5)</td>
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<tr>
<td>10 to 90th percentile</td>
<td>186</td>
<td>1.0</td>
<td></td>
<td>39</td>
<td>1.0</td>
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<tr>
<td>≥90th percentile</td>
<td>20</td>
<td>0.97 (0.61 to 1.5)</td>
<td>0.9</td>
<td>5</td>
<td>1.1 (0.45 to 2.9)</td>
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<tr>
<td>Men</td>
<td></td>
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<tr>
<td>&lt;10th percentile</td>
<td>21</td>
<td>1.7 (1.1 to 2.8)</td>
<td>0.02</td>
<td>2</td>
<td>1.3 (0.29 to 5.5)</td>
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<td>10 to 90th percentile</td>
<td>107</td>
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<td>14</td>
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<tr>
<td>≥90th percentile</td>
<td>12</td>
<td>1.0 (0.56 to 1.8)</td>
<td>1.0</td>
<td>2</td>
<td>1.3 (0.29 to 5.6)</td>
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<td>Women</td>
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<tr>
<td>&lt;10th percentile</td>
<td>11</td>
<td>1.2 (0.63 to 2.2)</td>
<td>0.6</td>
<td>5</td>
<td>1.7 (0.66 to 4.5)</td>
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<tr>
<td>10 to 90th percentile</td>
<td>79</td>
<td>1.0</td>
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<td>25</td>
<td>1.0</td>
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<tr>
<td>≥90th percentile</td>
<td>8</td>
<td>0.91 (0.44 to 1.9)</td>
<td>0.8</td>
<td>3</td>
<td>1.1 (0.33 to 3.6)</td>
</tr>
</tbody>
</table>

Low birth weight increases risk for ESRD.
Fetal programming of renal function

Jörg Dötsch · Christian Plank · Kerstin Amann

Also experimental models of immune mediated acquired glomerular diseases are worse in animals with low birth weight induced by uterine arterial ligation.

Received: 9 November 2010 / Revised: 9 December 2010 / Accepted: 15 December 2010
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Developing programming

several diseases in adult age have their origin in a dysegulated developing programming during the in utero life due to defective nutritional apports or noxious agents exposure

Pregnancy and prenatal life are critical for the renal function and the cardiovascular risk
• The nefrogenesis is not complete till the 36° weeks of gestation.
• The growth after a preterm birth (even in intensive care units) allows < 10% only of the expected renal growth in respect to in utero growth in regular term infants.
Environmental conditioning of genetical factors: the mother acts as the organogenesis conditioning environment.
The Clinical Importance of Nephron Mass

Valerie A. Luyckx* and Barry M. Brenner†

*Division of Nephrology and Immunology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; and †Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts
<table>
<thead>
<tr>
<th>Experimental Model</th>
<th>Proposed Mechanism of Nephron Number Reduction</th>
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<tbody>
<tr>
<td>Maternal low-protein diet</td>
<td>↑ apoptosis in metanephros and postnatal kidney</td>
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<tr>
<td></td>
<td>Altered gene expression in developing kidney</td>
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<tr>
<td></td>
<td>Altered gene methylation</td>
</tr>
<tr>
<td></td>
<td>↓ placental 11-βHSD2 expression</td>
</tr>
<tr>
<td></td>
<td>↓ branching of ureteric bud</td>
</tr>
<tr>
<td>Maternal vitamin A restriction</td>
<td>? maintenance of spatial orientation of vascular development</td>
</tr>
<tr>
<td></td>
<td>↓ c-ret expression</td>
</tr>
<tr>
<td>Maternal iron restriction</td>
<td>? reduced oxygen delivery</td>
</tr>
<tr>
<td></td>
<td>? altered glucocorticoid responsiveness</td>
</tr>
<tr>
<td></td>
<td>? altered micronutrient availability</td>
</tr>
<tr>
<td>Gestational glucocorticoid exposure</td>
<td>↑ fetal glucocorticoid exposure</td>
</tr>
<tr>
<td></td>
<td>? enhanced tissue maturation</td>
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<tr>
<td></td>
<td>↑ glucocorticoid receptor expression</td>
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<td></td>
<td>↑ 1α- and β-ATPase expression</td>
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<td></td>
<td>↓ renal and adrenal 11-βHSD2 expression</td>
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<td>Uterine artery ligation/embolization</td>
<td>↑ proapoptotic gene expression</td>
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<td>↓ antiapoptotic gene expression</td>
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<td>Altered gene methylation</td>
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<td></td>
<td>Altered renin-angiotensin gene expression</td>
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<tr>
<td>Maternal diabetes/hyperglycemia</td>
<td>↓ IGF-11/mannose-6-phosphate receptor expression</td>
</tr>
<tr>
<td></td>
<td>Altered IGF-11 activity/bioavailability</td>
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<tr>
<td></td>
<td>Activation of NF-κB</td>
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<td>Gestational drug exposure</td>
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<tr>
<td>gentamicin</td>
<td>↓ branching morphogenesis</td>
</tr>
<tr>
<td>β lactams</td>
<td>↑ mesenchymal apoptosis</td>
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<tr>
<td>cyclosporine</td>
<td>Arrest of nephron formation</td>
</tr>
<tr>
<td>ethanol</td>
<td>? via reduced vitamin A levels</td>
</tr>
<tr>
<td>COX2 inhibitors</td>
<td>Affects prostaglandins</td>
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</tbody>
</table>
Low neonatal birth weight

Brenner’s hypothesis in the ’80s:
- Low nephron number,
- Glomerular hyperfiltration,
- Genic activation

Hypertrophic glomeruli
Glomerular hypertension

Reduced GFR
Renal sclerosis
Increased albuminuria

Birth weight <2.5 Kg increases by 40-70% the ESRD in adult life
To rule out the possibility of maternal confounding factors (smoking, hypertension, etc)

- Monozygous or dizygous twins differing from their birth weight were followed up:
  - a reduced intrauterine growth conditions CKD e and hypertension in adult age, independently from genetic and environmental factors
- At multivariate analysis the low birth weight remains the only independent risk factor
Is Low Birth Weight an Antecedent of CKD in Later Life? A Systematic Review of Observational Studies

Sarah L. White, MPH,¹ Vlado Perkovic, FRACP, PhD,¹ Alan Cass, FRACP, PhD,¹ Choon Lan Chang, PhD,² Neil R. Poulter, FRCP, MSc, PhD,² Tim Spector, FRCP, MD,³ Leigh Haysom, FRACP, PhD,⁴ Jonathan C. Craig, FRACP, PhD,⁴,⁵ Isa Al Salmi, FRACP, MD,⁶ Steven J. Chadban, FRACP, PhD,⁷ and Rachel R. Huxley, DPhil⁷

- 30 studies
- Informations from 39,559 subjects
Low Birth Weight and Risk of CKD

Odd Ratio: 1.73 (1.44-2.08) p<0.001

<table>
<thead>
<tr>
<th>Author</th>
<th>Country of origin</th>
<th>Year of publication</th>
<th>Participant sex</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
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<td>Albunsingua</td>
<td>Australia</td>
<td>NA</td>
<td>M &amp; F</td>
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<tr>
<td>Heysom</td>
<td>Singapore</td>
<td>2001</td>
<td>M &amp; F</td>
<td>2.09 (0.46, 9.55)**</td>
<td>6.31</td>
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<td>Rasmussen</td>
<td>Sweden</td>
<td>1998</td>
<td>M &amp; F</td>
<td>2.77 (0.77, 9.95)*</td>
<td>8.29</td>
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<td>Vasanrhelyi</td>
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<td>Yudkin</td>
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<td>3.10 (0.87, 10.98)**</td>
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<td>Nelson</td>
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<td>9.68</td>
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<td>Painter</td>
<td>Netherlands</td>
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<td>M &amp; F</td>
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<td>13.95</td>
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<td>Hoy</td>
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<td>15.28</td>
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<td>M &amp; F</td>
<td>0.99 (0.61, 1.61)**</td>
<td>23.47</td>
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<tr>
<td>ESKD</td>
<td></td>
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<td></td>
<td>1.81 (1.19, 2.77)**</td>
<td>100.00</td>
</tr>
<tr>
<td>Dyck</td>
<td>Canada</td>
<td>2003</td>
<td>M &amp; F</td>
<td>1.62 (0.88, 2.97)*</td>
<td>8.22</td>
</tr>
<tr>
<td>Fan</td>
<td>USA</td>
<td>2006</td>
<td>M &amp; F</td>
<td>1.56 (1.02, 2.39)**</td>
<td>16.69</td>
</tr>
<tr>
<td>Vikeo</td>
<td>Norway</td>
<td>2006</td>
<td>M &amp; F</td>
<td>2.00 (1.41, 2.83)**</td>
<td>25.19</td>
</tr>
<tr>
<td>Lackland</td>
<td>USA</td>
<td>2000</td>
<td>M &amp; F</td>
<td>1.40 (1.09, 1.79)**</td>
<td>48.90</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.4)</td>
<td></td>
<td></td>
<td></td>
<td>1.58 (1.33, 1.88)</td>
<td>100.00</td>
</tr>
<tr>
<td>Low eGFR and other CKD</td>
<td></td>
<td></td>
<td></td>
<td>3.66 (1.80, 7.43)**</td>
<td>8.96</td>
</tr>
<tr>
<td>Al Salim</td>
<td>Australia</td>
<td>2007</td>
<td>M &amp; F</td>
<td>1.08 (0.55, 2.12)**</td>
<td>9.39</td>
</tr>
<tr>
<td>Hallan</td>
<td>Norway</td>
<td>2008</td>
<td>Males</td>
<td>2.35 (1.30, 4.24)**</td>
<td>10.43</td>
</tr>
<tr>
<td>Al Sales</td>
<td>Australia</td>
<td>2007</td>
<td>Males</td>
<td>3.40 (2.13, 5.62)**</td>
<td>12.15</td>
</tr>
<tr>
<td>Al Salim</td>
<td>Australia</td>
<td>2007</td>
<td>Females</td>
<td>2.04 (1.45, 2.88)**</td>
<td>13.88</td>
</tr>
<tr>
<td>Poultier</td>
<td>UK</td>
<td>NA</td>
<td>Females</td>
<td>1.31 (0.97, 1.78)**</td>
<td>14.51</td>
</tr>
<tr>
<td>Li</td>
<td>USA</td>
<td>2008</td>
<td>Males</td>
<td>1.65 (1.24, 2.20)**</td>
<td>14.62</td>
</tr>
<tr>
<td>Li</td>
<td>USA</td>
<td>2008</td>
<td>Females</td>
<td>1.07 (0.92, 1.25)**</td>
<td>16.04</td>
</tr>
<tr>
<td>Subtotal (I-squared = 83.5%, p &lt; 0.001)</td>
<td></td>
<td></td>
<td></td>
<td>1.79 (1.31, 2.45)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p = 0.4
Overall (I-squared = 65.3%, p < 0.001)

1.73 (1.44, 2.08)

NOTE: Weights are from random effects analysis
CARDIO-RENAL PREVENTION
Consequences of Fetal Programming for Cardiovascular Disease in Adulthood

LOPA LEACH* AND GIOVANNI E. MANN†

*Cardiovascular Research Group, School of Biomedical Sciences, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham,
Developmental programming and hypertension

Anne Monique Nuyt\textsuperscript{a} and Barbara T. Alexander\textsuperscript{b}

\textsuperscript{a}Departments of Pediatrics and Physiology, Research Center, CHU Sainte-Justine, Université de Montréal, Canada

\textsuperscript{b}Department of Physiology and Biophysics, University of Mississippi Medical Center Jackson, MS, USA

<table>
<thead>
<tr>
<th>Programmed Characteristic</th>
<th>Proposed Mechanism/Evidence Affecting BP in Programmed Offspring versus Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced nephron number</td>
<td>↓ flow-mediated dilation in LBW children</td>
</tr>
<tr>
<td></td>
<td>↑ uric acid</td>
</tr>
<tr>
<td></td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td></td>
<td>Impaired vascular structure and capillary density</td>
</tr>
<tr>
<td>Altered vascular reactivity</td>
<td>Administration of inhibitors of RAS abrogates later hypertension</td>
</tr>
<tr>
<td></td>
<td>Administration of angiotensin II causes increased hypertensive response</td>
</tr>
<tr>
<td>Altered RAS</td>
<td>↓ renal renin levels</td>
</tr>
<tr>
<td></td>
<td>↓ renal renin gene expression</td>
</tr>
<tr>
<td></td>
<td>↓ renal renin enzyme activity</td>
</tr>
<tr>
<td>Altered sodium handling</td>
<td>↓ fractional excretion of sodium</td>
</tr>
<tr>
<td></td>
<td>↑ expression of BSC1 and TSC</td>
</tr>
<tr>
<td></td>
<td>↑ expression of glucocorticoid receptor</td>
</tr>
<tr>
<td></td>
<td>↑ expression of glucocorticoid responsive α1 and β1 subunits of Na/K-ATPase</td>
</tr>
<tr>
<td></td>
<td>↑ expression of NHE3</td>
</tr>
<tr>
<td></td>
<td>↑ expression of β and γ ENaC</td>
</tr>
<tr>
<td>Increased sympathetic nervous system activity</td>
<td>Renal denervation reduced systolic BP and sodium transporter expression</td>
</tr>
<tr>
<td>Catch-up growth/obesity</td>
<td>Higher BP in children who catch up fastest</td>
</tr>
<tr>
<td></td>
<td>Reduced flow-mediated dilation with higher rate of weight gain</td>
</tr>
</tbody>
</table>
- Reduced number of glomeruli
- Increased Na reabsorption from distal tubuli (NCC and E-NaC)
- RAS
- Increased Na sensitivity
- Cortisol-mineralcorticoid receptor
- Sympatic activity:
  - HIF is activated by hypoxia, Na is reabsorbed
Exaggerated maternal sodium intake is an epigenetic conditioning factor for hypertension

- eNOS decrease
- ADMA increase
- Reactive oxygen species production
- Endothelial proliferation
increased risk for children with low birth weight
several adults have a certain degree of CKD derived from congenital causes, which will never end in dialysis need but represent a severe risk for cardiovascular accidents
• Children with low neonatal birth weight present with a normal BP at birth,
• But at adolescence they have 2-3 mmHg BP higher than controls
• If they become obese, hypertension is further enhanced
Obesity and preterm birth: additive risks in the progression of kidney disease in children

Carolyn L. Abitbol • Jayanthi Chandar • Maria M. Rodríguez • Mariana Berho • Wacharee Seeherunvong • Michael Freundlich •

Fig. 1 Kaplan–Meier actuarial renal survival curves in four groups of children with kidney disease. Obese-PT patients had increased risk of renal demise during childhood compared with Obese-T (hazard ratio 2.4; 95% CI 1.1 to 7.1 P = 0.04) with median renal survival of 15 years of age for Obese-PT compared with 23 years for Obese-T patients.
Obesity, albuminuria and urinalysis findings in US young adults from the add health wave III study
Ferris M et al clin JASN 2007; 2: 1207-1214

18-26 years old
15,000 subjects
6 years of follow-up

BMI >35 kg/m2 or increase in BMI during follow-up
Is associated with proteinuria OR 1.76 (1.02-3.04)
Figure 2. Prevalence of albuminuria (unadjusted) by class II obesity (body mass index [BMI] ≥35 kg/m²) versus all others (BMI <35 kg/m²) by race/ethnicity and sex groups.
The Lede

Blogging the News With Robert Mackey

March 8, 2007, 9:42 AM

Into the Mouths of Babes: Childhood Obesity

By TOM ZELLER JR
Obesity, albuminuria and urinalysis findings in US young adults from the add health wave III study
Ferris M et al clin JASN 2007; 2: 1207-1214

18-26 yo;
15,000 subjects
Observation over 6 years

6:1000
6000/milion young subject have proteinuria (in 1/6 associated with hematuria)

27:1000
27,000/milion subjects have hematuria without urinary tract infection
Is young adult underdiagnosed for Glomerular diseases?

Urinalysis
N=9,371

0.6% proteinuria
2.7% hematuria
0.1% proteinuria and hematuria

RBC > 25 Ery/μL
n=432 (4.6%)

Proteinuria > 30mg/dL
n=73 (0.8%)
CKD in children

- unsuspectedly reduced renal mass
- undiagnosed glomerular diseases

Short-term outcome (childhood): dialysis, transplantation

Renal mass reduction

Chronic glomerular diseases

Long-term outcome in adult and elderly patients
CRF without diagnosis in all the renal registries

account for about 30% of all patients entering dialysis

we need an early diagnosis starting from a very early time
sia nel bambino che nell’adulto

Basso peso neonatale

identificazione precoce di soggetti a rischio: sorveglianza attenta

Rischio di malattia CV

Rischio di CKD
In adults in 2007
28% CRF without diagnosis
UK registries

Underdiagnosed
CAKUT
or
Glomerular diseases?
Considerando la progressione generale della IgAN
(25% dei casi necessitano dialisi entro 20 anni)
67% dei casi di IgAN che arrivano alla dialisi hanno età di 25-55 anni
(25% hanno < 30 anni all’inizio del RDT)
è evidente che

molte IgAN che progrediscono alla dialisi nell’adulto cominciano nell’età pediatrica
Primary IgAN

- Chronic renal failure
- Normal renal function
- Proteinuria and microscopic hematuria
- ++ Hb
- macroscopic hematuria
- No urinary signs

years 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Patient A: hematuria detected by screening children

Patient B: proteinuria

Patient C: hypertension, reduced GFR

Start of IgA deposition

Geddes NDT 2003
Italian Registry of Pediatric Renal Biopsies (432 cases)

Children with isolated microscopic hematuria (A) or with hematuria associated with proteinuria (B)

*Coppo et al Nephrol Dial Transplant 1998; 13: 293-297*
La IgAN è la più comune glomerulonefrite in Italia ed ha spesso radici nell’età pediatrica

IgAN nel giovane: reperto orinario è spesso modesto, microematuria e proteinuria in tracce  
(che talora restano, note, per tutta la vita ma senza adeguato follow-up)

Molti casi non sono diagnosticati per le loro minime manifestazioni cliniche  
(che spesso restano, non note, per tutta la vita)

Nella ricerca di fattori di rischio per CKD e CVD  
Non trascuriamo il più banale: microematuria e GN cronica non diagnosticata
RIDT 2008: malattia causale ingresso in dialisi

22% senza diagnosi di malattia causale,
23% con diagnosi generica di malattia vascolare
20% nefropatia diabetica, senza biospia renale
In RECORD-IT 30% glomerulonefriti croniche in CKD
In ERA-EDTA Registry 32% glomerulonefriti
Il 30% dei trapiantati ha una malattia glomerulare.

L’arrivo alla dialisi ed al trapianto senza diagnosi rappresenta un risultato molto povero,
accettabile solo se fossimo certi che l’intervento del nefrologo non sarebbe in ogni caso servito a nulla.

Questo è nichilismo inaccettabile, che si ribalta in una svalutazione della nostra Professione.
Impariamo dai Diabetologi

Diagnosi precoce

Legacy effect
Effetto memoria della terapia precoce
Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes


Medical Hypotheses 73 (2009) 73–79

Late effect of treatment for reducing cardiovascular risk – A hypothesis on cardiometabolic therapeutic memory

György Jermendy *
UKPDS and the Legacy Effect
John Chalmers, M.D., Ph.D., and Mark E. Cooper, M.D., Ph.D.

The United Kingdom Prospective Diabetes Study (UKPDS) continues to produce important evidence concerning the evolution of type 2 diabetes and its management. Two studies published in this issue of the Journal provide some answers to two questions of fundamental importance to patients with diabetes and to physicians alike. In one article, Holman et al. (UKPDS 80) provide data that confirm a so-called legacy effect associated with intensive glucose control in patients with type 2 diabetes, long after the cessation of randomized intervention. This finding provides a fitting parallel to the observations of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) study in patients with type 1 diabetes. In the other article, Holman et al. (UKPDS 81) present the opposite conclusion with respect to blood pressure, reporting that there is no such sustained effect with intensive control of blood pressure and that good blood-pressure control must be continued if the benefits are to be maintained.

In the original UKPDS, which involved 5102 patients with newly diagnosed type 2 diabetes, 4209 patients were randomly assigned to receive either conventional therapy (diet alone) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control, whereas 1148 patients who also had hypertension were randomly assigned to tight or less-tight regimens for blood-pressure control. In post-trial monitoring, patients returned to community- or hospital-based diabetes care with no attempt to maintain their previously randomized therapies. Patients were seen annually for
Intensive Glucose Control and Cardiovascular Outcomes in Type 2 Diabetes (April 2010)

Richard J. MacIsaac, FRACP* and George Jerums, FRACP

Endocrine Centre and Department of Medicine, Austin Health and University of Melbourne, Australia

**Fig. 1.** Results of the United Kingdom Prospective Study (UKPDS) follow-up started after the completion of the randomised intensive glucose-lowering arm of the study. NS, Not significant. Relative Risk Reduction and p values refer to the differences observed for patients randomised to intensive versus less intensive glycaemic control.
Il rischio cardiovascolare aumenta con l’aumento della proteinuria anche per valori minimi di microalbuminuria

(*) Gerstein, JAMA (2001) 268:421

PERCHE’ HANNO MICROALBUMINURIA?
Microalbuminuria

Diabete

Ipertensione

Glomerulonefriti pre-cliniche

Riduzione cronica di parenchima renale
CKD in children

unsuspectedly reduced renal mass

undiagnosed glomerular diseases

short-term outcome (childhood): dialysis, transplantation

renal mass reduction

chronic glomerular diseases

long-term outcome in adult and elderly patients
LINEE DI ATTIVITA’
PROGRAMMA SIN 2010-2012

Migliorare l’immagine della Nefrologia Italiana

Migliorare la visibilità del lavoro del Nefrologo
Migliorare la visibilità SIN attraverso i risultati
Migliorare la cura dei pazienti con malattia di rene
PROGRAMMA 2010-2012

PROGETTI SIN
• La diagnosi precoce di malattia renale
• Il paziente portatore di rene trapiantato
• La dialisi come sistema integrato con la nefrologia
La prevenzione della CKD fin dalle prime età (il controllo dietetico-farmacologico dove possibile) significa prevenzione di dialisi e di rischio CV nell’adulto.
CKD in children

renal mass reduction

chronic glomerular diseases

short-term outcome (childhood): dialysis, transplantation

long-term outcome in adult and elderly patients
Renal replacement therapy in children: data from 12 registries in Europe

Data from 12 registries in Europe

children and adolescents survival in dialysis

Survival Probability

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Years Since Start Dialysis

1995-2000
1990-1994
1985-1989
1980-1984

AHR (95% CI)
0.64 (0.41-1.00)
0.60 (0.40-0.91)
0.83 (0.57-1.23)
reference

children and adolescents survival after 1st renal transplantation

Survival Probability

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Years Since First Transplant

1995-2000
1990-1994
1985-1989
1980-1984

AHR (95% CI)
0.58 (0.34-1.00)
0.54 (0.34-0.85)
0.87 (0.60-1.27)
reference
Renal replacement therapy in children: data from 12 registries in Europe

Fig. 6 Causes of death by treatment modality (1980–2000) (CVA cerebrovascular accident)
USRDS database (Medicare)

1380 deaths over 130,000 patients at risk in 1990-1996

MORTALITY due to CVD in children with ESRF:

DIALYSIS: 1000 times more than general population

TRANSPLANT: 100 times more than general population of the same age
Clinical Science Articles

Reduced Systolic Myocardial Function in Children with Chronic Renal Insufficiency

Marcello Chinali,* Giovanni de Simone,* Maria Chiara Matteucci,† Stefano Picca,† Antonio Mastrostefano,† Ali Anarat,‡ Salim Çaliskan,§ Nikola Jeck,‖ Thomas J. Neuhaus,‖ Amira Peco-Antic,** Licia Peruzzi,†† Sara Testa,‡‡ Otto Mehls,§§ Elke Wühl,§§ and Franz Schaefer,§§ for the ESCAPE Trial Group
Systolic dysfunction in 48% of the cases with concentric LVH

---

**Figure 2.** Percentage of patients with impaired systolic function according to LV geometry (concentric versus eccentric versus normal geometry) in children with CRI (n = 130).
LVMI is correlated with CKD.
Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease

Mieczyslaw Litwin¹, Elke Wühl², Claudia Jourdan³, Anna Niemirska¹, Jens P. Schenk³,², Katarzyna Jobs¹, Ryszard Grenda¹, Zbigniew T. Wawer¹, Pawel Rajszys⁴, Otto Mehls² and Franz Schaefer²
Evolution of IMT in children
Coronary artery calcifications in children with end-stage renal disease
Coronary artery calcifications in children with end-stage renal disease

Fig. 1 Multidetector spiral computed tomography section from a 14-year-old male hemodialysis patient with extensive calcification in all four coronary arteries (total CAC score was determined to be 4332 Agatston units). In the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) calcification can be seen (arrows). RV right ventricle, RA right atrium, LV left ventricle, LA left atrium
CKD in children

unsuspectedly reduced renal mass

undiagnosed glomerular diseases

short-term outcome (childhood): dialysis, transplantation

renal mass reduction

chronic glomerular diseases

long-term outcome in adult and elderly patients
Left Ventricular Geometry in Children with Mild to Moderate Chronic Renal Insufficiency

Maria Chiara Matteucci,* Elke Wühl,† Stefano Picca,* Antonio Mastrostefano,* Gabriele Rinelli,* Carmela Romano,‡ Gianfranco Rizzoni,* Otto Mehl,’ Giovanni de Simone,‡ Franz Schaefer; and ESCAPE Trial Group

LVMI correlato a CKD

Figure 1. Distribution of left ventricular mass index (LVMI) and relative wall thickness (RWT) in 156 children with chronic renal insufficiency (CRI). Reference lines indicate 95th percentiles of LVMI and RWT in healthy control populations (18).
Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease

Mieczyslaw Litwin¹, Elke Wühl², Claudia Jourdan³, Anna Niemirska¹, Jens P. Schenk³,², Katarzyna Jobs¹, Ryszard Grenda¹, Zbigniew T. Wawer¹, Pawel Rajzys⁴, Otto Mehls² and Franz Schaefer²
PROCEEDINGS OF THE 2009 PEDIATRIC NEPHROLOGY FELLOWS CONFERENCE

Early Origins of Cardiovascular Disease in Pediatric Chronic Kidney Disease

Hiren P. Patel
Department of Pediatrics, Nationwide Children’s Hospital, The Ohio State University College of Medicine, Columbus, Ohio, USA
il rischio CV di un soggetto di 25 anni trapiantato di rene è simile a quello di uno di 55 anni senza nefropatie

il rischio di IMA in un soggetto di 18-30 anni è 2.7% nei primi 3 anni dopo il trapianto
Hypertension and CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage1</td>
<td>35.9%</td>
</tr>
<tr>
<td>Stage2</td>
<td>57.6%</td>
</tr>
<tr>
<td>Stage3</td>
<td>79.8%</td>
</tr>
<tr>
<td>Stage4</td>
<td>91.6%</td>
</tr>
<tr>
<td>Stage5</td>
<td>91.1%</td>
</tr>
<tr>
<td>GFR ≥60</td>
<td>44.9%</td>
</tr>
<tr>
<td>GFR &lt;60</td>
<td>80.3%</td>
</tr>
</tbody>
</table>
Treat the **kidney** to protect your **heart**!

*de Zeeuw, 2004*

Prevenire le malattie di rene significa ridurre necessità di dialisi e trapianto ma anche morbilità e mortalità per danno cardiovascolare.

cominciare quando tutto il processo è avanzato può essere tardi!
Le insufficienze croniche di organo sono in pediatria una patologia rara se si considera la fase terminale con necessità di trapianto.

Nell’adulto le insufficienze d’organo sono patologie gravi per frequenza e impegno economico-sociale.

Molte malattie croniche che conducono ad insufficienza d’organo nell’adulto hanno radici molto lontane, nel 20% dei casi nell’infanzia.

Necessità di conoscenza del problema per
- diagnosi precoce
- terapia ottimale per rallentare l’evoluzione

La CKD aumenta il rischio CV
Le malattie renali croniche iniziate in età pediatrica aumentano il rischio CV nell’adulto?

E’ possibile una prevenzione di rene e di vita che si inizi in età pediatrica?
Task Force in USA NIH nelle malattie renali dei bambini in insufficienza renale cronica
Gennaio 2006

studio prospettico dei bambini in IRC

morbilità correlata alla IRC

Malattia cardiovascolare
malattia ossea
Ipertensione
Anemia
Inflamazione
Crescita
Funzione neurocognitiva
Sviluppo neuro-psichico
Stato socio-economico familiare
La prevenzione di CKD deve iniziare fin dall’età pediatrica: il 20% della CKD dell’adulto ha origine in età pediatrica.

Il rischio CV dell’adulto ha radici in età pediatrica.
Pazienti prevalenti suddivisi per classi di età e modalità di terapia sostitutiva (RIDT 31/12/2004)
Renal replacement therapy in children: data from 12 registries in Europe

**INCIDENZA:** età 0-19

**PREVALENZA:** età 0-19
Long-term outcome of chronic dialysis in children

Children starting dialysis ≥5 years age
n = 44

Children starting dialysis < 5 years age
n = 54

Trends in treatment and outcomes of survival of adolescents initiating end-stage renal disease care in the United States of America

Casistica Great Hormond Street Hospital, Londra 1984-1998

Casistica USA, USRDS 1976-1993
### Prevalenza di IRC in età pediatrica in Piemonte

**in press: Acta pediatrica 2008**

<table>
<thead>
<tr>
<th>Quadrante</th>
<th>Numero di individui di età &lt;18 anni*</th>
<th>Numero di pazienti con patologia renale per ogni quadrante</th>
<th>Prevalenza della patologia renale in ogni quadrante</th>
<th>Prevalenza media in tutta la Regione</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>332238</td>
<td>41</td>
<td>41/332238 → 12.3/1000000 abitanti</td>
<td>9.6/1000000 abitanti</td>
</tr>
<tr>
<td>II</td>
<td>125028</td>
<td>13</td>
<td>13/125028 → 10.4/1000000 abitanti</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>91696</td>
<td>9</td>
<td>9/91696 → 9.8/1000000 abitanti</td>
<td></td>
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<tr>
<td>IV</td>
<td>84006</td>
<td>5</td>
<td>5/84606 → 5.9/1000000 abitanti</td>
<td></td>
</tr>
</tbody>
</table>

*Dati BDDE anno 2003 (per Torino CSI anno 2000)*

96 casi per milione di soggetti della stessa età
Nuovi pazienti in Italia suddivisi per fasce d’età

<table>
<thead>
<tr>
<th>Anno</th>
<th>DP 0-15.9 anni</th>
<th>DP 16-18 anni</th>
<th>HD 0-15.9 anni</th>
<th>HD 16-18 anni</th>
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<tbody>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Independent predictors of LV geometry in pediatric patients with CRI

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Predictor</th>
<th>β</th>
<th>P</th>
<th>R²</th>
<th>Cum:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log LVMI</td>
<td>Hemoglobin</td>
<td>−0.221</td>
<td>0.0003</td>
<td>0.107</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI SDS</td>
<td>0.173</td>
<td>0.005</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>−0.209</td>
<td>0.04</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR</td>
<td>−0.194</td>
<td>0.04</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>RWT</td>
<td>Albumin</td>
<td>0.225</td>
<td>0.04</td>
<td>0.045</td>
<td>0.227</td>
</tr>
<tr>
<td></td>
<td>BMI SDS</td>
<td>0.173</td>
<td>0.09</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phosphate</td>
<td>0.171</td>
<td>0.10</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>LVEDD</td>
<td>Age</td>
<td>−0.274</td>
<td>&lt;0.0001</td>
<td>0.119</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin</td>
<td>−0.137</td>
<td>0.005</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI SDS</td>
<td>0.137</td>
<td>0.05</td>
<td>0.024</td>
<td></td>
</tr>
</tbody>
</table>

*Results of stepwise linear regression analysis. LVEDD, LV end-diastolic diameter.*
Figure 1. Relationship between fractional shortening (FS%) and midwall shortening (mS%) in normal control subjects (●, solid line) and children with chronic renal insufficiency (CRI) and nonconcentric (◇, dotted line) or concentric (stars, dashed line) left ventricular (LV) geometry.
La funzione sistolica è alterata nonostante l'aumento della massa VS

ESCAPE trial europeo.
156 bambini 3-18 anni, CKD 2-4

La funzione sistolica è alterata nonostante l'aumento della massa VS

la disfunzione sistolica è più comune nei bambini con ipertrofia VS concentrica ed associata con valori di Hb minori
NONINVASIVE ARTERIAL FUNCTION ASSESSMENT

(A) \[ A_1 = \frac{\Delta P}{P_{\text{PP}}} \times 100 \]

(B) \[ A_2 = \frac{P_2}{P_1} \times 100 \]
Per evitare la dialisi a soggetti adulti:

Molte nefropatie in età pediatrica sono considerate benigne ma in realtà progrediscono decenni dopo

Rischio CV
Questo è 20 volte maggiore del normale e causa la morte nel 25% dei bambini o ex bambini in dialisi e nel 15% dei trapiantati in età pediatrica
Disfunzione sistolica subclinica in bambini con CKD iniziale o moderata. Questa condizione è associata negli adulti a prognosi CV sfavorevole.

Correlazione fra disfunzione VS e velocità di progressione della IRC (iperattività simpatica o del sistema RAS a livello tissutale?)
Tutti gli indici sono maggiori del normale in CKD e peggiorano in dialisi.

Parziale miglioramento dopo trapianto, Correlata alla durata della dialisi ed al danno pre-esistente
La sopravvivenza del rene trapiantato nei giovani è aumentata ma il rischio CV di un giovane portatore di rene trapiantato è 100 volte quello dei coetanei sani

Fattori di rischio comuni: ipertensione, obesità, IVS, diabete, iperlipidemia, Fattori di rischio infiammatorio, CKD, Ca/P
tutti i fattori precedenti, sia in osservazioni umane che in modelli animali

Basso peso neonatale

Rischio di intolleranza glucosio

Rischio di dislipemia

Rischio di ipertensione

Rischio di malattia CV

Rischio di CKD
The Clinical Importance of Nephron Mass

Valerie A. Luyckx* and Barry M. Brenner†
Perinatal Programming

Immediate Effects

Intrauterine deficiency or surplus

High or low birth weight

Step 1: Direct damage of the fetus by pathological programming

"Mismatch"

Step 2: Secondary damage by mismatch between postnatal and prenatal environment

Phenotype of perinatal programming

Fig. 2 Steps in prenatal programming of renal disease
Assessment of long-term renal complications in extremely low birth weight children

Przemko Kwinta • Małgorzata Klimek • Dorota Drozdz • Andrzej Grudzień • Mateusz Jagła • Magdalena Zasada • Jacek Jozef Pietrzyk

Received: 7 December 2010 / Revised: 20 February 2011 / Accepted: 24 February 2011
### Table 1  Baseline characteristics of extremely low birth weight (ELBW) participants\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, median (25th–75th percentile)</td>
<td>890 g (760–950)</td>
</tr>
<tr>
<td>Gestational age, median (25th–75th percentile)</td>
<td>27 weeks (26–29)</td>
</tr>
<tr>
<td>5-min Apgar score, median; (25th–75th percentile)</td>
<td>6 (5–7)</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>31 (47)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>77 (91)</td>
</tr>
<tr>
<td>Surfactant administration</td>
<td>57 (73)</td>
</tr>
<tr>
<td>PDA ligation</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage grade III–IV</td>
<td>8 (10.2)</td>
</tr>
<tr>
<td>Oxygen at 36 weeks postmenstrual age</td>
<td>30 (38)</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>36 (46)</td>
</tr>
<tr>
<td>Confirmed sepsis</td>
<td>16 (20.5)</td>
</tr>
<tr>
<td>Weight gain during NICU stay (g/week), mean (SD)</td>
<td>146 (102)</td>
</tr>
<tr>
<td>Length of hospitalization, median (25th–75th percentile)</td>
<td>77 (55–103)</td>
</tr>
</tbody>
</table>

\(^a\) Expressed as a number (percentage) of patients unless otherwise indicated; PDA patent ductus arteriosus; NICU neonatal intensive care unit
Table 4 Secondary outcome variables in the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>ELBW group (n=78)</th>
<th>Control group (n=38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cystatin C level (mg/l)</td>
<td>0.64 (0.07)</td>
<td>0.59 (0.07)</td>
<td>0.01&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Albuminuria (mg/g creatinine)</td>
<td>5.53 (3.9)</td>
<td>4.9 (3.3)</td>
<td>0.5&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>24-h mean MAP (mmHg)</td>
<td>79 (5.9)</td>
<td>77 (4.4)</td>
<td>0.2&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day-time mean MAP (mmHg)</td>
<td>82 (5.8)</td>
<td>80 (4.8)</td>
<td>0.4&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Night-time mean MAP (mmHg)</td>
<td>75 (5.7)</td>
<td>73 (4.3)</td>
<td>0.26&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>24-h mean MAP (z-score)</td>
<td>0.5 (1.1)</td>
<td>-0.3 (0.78)</td>
<td>0.1&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day-time mean MAP (z-score)</td>
<td>-0.36 (0.9)</td>
<td>-0.7 (0.73)</td>
<td>0.5&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Night-time mean MAP (z-score)</td>
<td>1.15 (0.84)</td>
<td>0.2 (0.72)</td>
<td>0.02&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Night-time dipping (%)</td>
<td>12 (6.5)</td>
<td>15 (4.5)</td>
<td>0.1&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Night-time dipping&lt;10%</td>
<td>13 (16.7%)</td>
<td>2 (5.2%)</td>
<td>0.13&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP load (%)</td>
<td>28 (22)</td>
<td>16 (14)</td>
<td>&lt;0.01&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>54</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>30–50%</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP load (%)</td>
<td>27 (20)</td>
<td>17 (10)</td>
<td>&lt;0.01&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic BP load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>55</td>
<td>34</td>
<td>0.04&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>30–50%</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Absolute kidney volume (ml)</td>
<td>81 (20)</td>
<td>113 (29)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Relative kidney volume (%)</td>
<td>85 (17)</td>
<td>97 (17)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Expressed as a mean and SD

<sup>p</sup> value for Student's t test<sup>b</sup>, Fisher's exact test<sup>c</sup>, Chi-square test<sup>d</sup>

MAP mean arterial pressure during 24-h ambulatory blood pressure measurement; BP blood pressure; ELBW extremely low birth weight
Prematurity, small for gestational age and perinatal parameters in children with congenital, hereditary and acquired chronic kidney disease

Doris Franke¹, Sina Völker¹, Sanny Haase¹, Leo Pavičić³, Uwe Querfeld², Jochen H.H. Ehrich¹ and Miroslav Živičnjak¹
Adverse consequences of accelerated neonatal growth: cardiovascular and renal issues

Umberto Simeoni • Isabelle Ligi • Christophe Buffat • Farid Boubred

Table 2 Renal consequences of neonatal growth in normal birth weight rat offspring. While accelerated neonatal growth induces renal injury, slow postnatal growth preserves long-term renal function.

<table>
<thead>
<tr>
<th>Studies</th>
<th>BW difference (%; vs control)</th>
<th>Nephron number difference (%; vs control)</th>
<th>GFR, AlbU (vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weaning</td>
<td>Adulthood</td>
<td></td>
</tr>
<tr>
<td>[147]a</td>
<td>-52%</td>
<td>-20% (10 months)</td>
<td>NE</td>
</tr>
<tr>
<td>[148]a</td>
<td>-40%</td>
<td>-25% (12 months)</td>
<td>NE</td>
</tr>
<tr>
<td>[69]b</td>
<td>-38%</td>
<td>-18% (2.5 months)</td>
<td>-25%</td>
</tr>
<tr>
<td>[70]b</td>
<td>+40%, +30%</td>
<td>+20% (12 months), +12% (12 months)</td>
<td>+25%, +20%</td>
</tr>
</tbody>
</table>
il rischio CV di un soggetto di 25 anni trapiantato di rene è simile a quello di uno di 55 anni senza nefropatie

il rischio di IMA in un soggetto di 18-30 anni è 2.7% nei primi 3 anni dopo il trapianto
A Project Funded by the European Union

5th Framework Program:

Quality of Life and Management of Living Resources
Key Action 7.2. Rare Degenerative Diseases

QL61-CT-2002-00908

Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure
LVH è il più importante indicatore di rischio CV nella popolazione generale ed in ESRD

ESCAPE trial europeo.
156 bambini 3-18 anni, CKD 2-4
Studiati con ECO cardio

Nei bambini mancano i fattori confondenti degli adulti: la malattia coronarica e la microangiopatia diabetica
Left Ventricular Geometry in Children with Mild to Moderate Chronic Renal Insufficiency

Maria Chiara Matteucci, Elke Wühl, Stefano Picca, Antonio Mastrostefano, Gabriele Rinelli, Carmela Romano, Gianfranco Rizzoni, Otto Mehl, Giovanni de Simone, Franz Schaefer; and ESCAPE Trial Group

Anomalie VS nel 43% dei bambini in CDK 2-4

22.3% alterazioni concentrifiche di geometria VS (ipertrofia o rimodellamento)

21% ipertrofica VS eccentrica.

Ipertrofia VS indipendente da Valori di PA
Terapia con ACEI
Malattia renale di base
LVMI correlato a CKD

Figure 1. Distribution of left ventricular mass index (LVMI) and relative wall thickness (RWT) in 156 children with chronic renal insufficiency (CRI). Reference lines indicate 95th percentiles of LVMI and RWT in healthy control populations (18).
Ipertrofia VS concentrica ed eccentrica come risultato di fattori emodinamici e non (CRP > 10mg/dl)

Sesso maschile, anemia, sovraccarico idrico, MBI, microinfiammazione, concorrono alla ipertrofia VS in bambini con IRC iniziale o moderata
Clinical Science Articles

Reduced Systolic Myocardial Function in Children with Chronic Renal Insufficiency

Marcello Chinali,* Giovanni de Simone,* Maria Chiara Matteucci,† Stefano Picca,† Antonio Mastrostefano,† Ali Anarat,‡ Salim Çaifiskan,§ Nikola Jeck,‖ Thomas J. Neuhaus,‖ Amira Peco-Antic,** Licia Peruzzi,†† Sara Testa,†† Otto Mehls,§§ Elke Wühl,§§ and Franz Schaefer,§§ for the ESCAPE Trial Group
Disfunzione sistolica nel 48% dei casi con IVS concentrica

Figure 2. Percentage of patients with impaired systolic function according to LV geometry (concentric versus eccentric versus normal geometry) in children with CRI (n = 130).
Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease

Mieczyslaw Litwin¹, Elke Wühl², Claudia Jourdan³, Anna Niemirska¹, Jens P. Schenk³, Katarzyna Jobs¹, Ryszard Grenda¹, Zbigniew T. Wawer¹, Pawel Rajszs², Otto Mehl² and Franz Schaefer²
Evolution of large-vessel arteriopathy
Litwin M et al NDT 2008; 14

Spessore intima-media (IMT)
area della sezione trasversa vasale (WCSA)
sezione trasversa del lume (LCSA)
rapportate all’età
Correlazione fra PA diastolica e IMT in bambini in CKD

Fig. 2. Standardized diastolic BP is associated with standardised IMT in paediatric patients.
Correlazione IMT carotidea normalizzata per età e sesso con assunzione di chelanti del fosforo e con CaxP

Figure 1. Correlation of carotid intima-media thickness (cIMT), normalized to SD score (SDS), with lifetime cumulative phosphate binder dose (in g/kg; left) and time-averaged mean serum calcium-phosphorus ion product (right). △, patients on dialysis treatment; ■, patients with a functioning renal allograft at time of examination.
Il rischio CV in bambini in CKD

E’causa la morte nel 25% dei bambini in dialisi

E’ causa di morte nel 15% dei soggetti trapiantati in età pediatrica
Evoluzione di IMT in bambini
Pulse wave velocity in end-stage renal disease: influence of age and body dimension

133 bambini e giovani 3-26 anni

PWV rapportata all’altezza staturale è aumentata in soggetti giovani in ESRD
Coronary artery calcifications in children with end-stage renal disease
Coronary artery calcifications in children with end-stage renal disease

Fig. 1 Multidetector spiral computed tomography section from a 14-year-old male hemodialysis patient with extensive calcification in all four coronary arteries (total CAC score was determined to be 4332 Agatston units). In the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) calcification can be seen (arrows). RV right ventricle, RA right atrium, LV left ventricle, LA left atrium
Coronary artery calcifications in children with end-stage renal disease

TAC spirale per indagare calcificazioni coronariche (CAC) in 53 bambini – giovani in ESRD

15% dei casi (11-21 anni) correlazione con: durata di dialisi, PTH, CaxP, Calcio per os, Vit D3
Renal replacement therapy in children: data from 12 registries in Europe

Data from 12 registries in Europe

- Survival in dialysis
- Survival after 1st renal transplantation

Graphs showing survival probability over years since start of dialysis and first transplantation.
Fig. 6 Causes of death by treatment modality (1980–2000) (CVA cerebrovascular accident)
Cardiovascular complications in pediatric end-stage renal disease

MORTALITA CV nei bambini con ESRF:

DIALISI: **1000 volte superiore** alla popolazione generale

TRAPIANTO: **100 volte superiore** alla popolazione generale della stessa età
PROTEINURIA

Angiotensin II

Afferent art

Efferent art
HEMODINAMIC EFFECTS

Angiotensina II

Vasoconstriction (↑ ET1, ↓ eNOS, ↓ ANP)

Glomerulare hyperfiltration

Hypertension

Proteinuria

(due to hemodynamic effects and modification of glomerular permeability)
Mitogen Activated Protein Kinases

ERK 1/2
- Elk-1/Sap1

p38 MAPK
- Elk-1/Sap1

JNK
- C-Jun

ATF-2

C-Jun

C-Fos

ELK-1/Sap1

NF-kB

IkB

AP-1

DNA

AP-1

IkB

NF-kB

MEK

C-Jun

C-Fos

ERK 1/2

JNK

p38 MAPK

Mitogen Activated Protein Kinases

ETS

Elk-1/Sap1

C-Jun

ATF-2

C-Fos
il rischio CV di un soggetto di 25 anni trapiantato di rene è simile a quello di uno di 55 anni senza nefropatie

il rischio di IMA in un soggetto di 18-30 anni è 2.7% nei primi 3 anni dopo il trapianto

Aspettativa di vita molto lunga:
necessità della massime misure di prevenzione possibili
Causes of ESRF in incident population

![Bar chart showing causes of ESRF in incident population across Japan, USA, Germany, and Australia. The chart uses different colors to represent different causes: red for GN, blue for diab neph, cyan for neph ang, and yellow for oth.]
IgAN in children

- Often detected only by **screening** urine tests, or analysis to sporting, or chance analysis.
IgAN in children

Linné, Berg, Levy, Hattori, Yoshikawa, Hogg, Wyatt

Estimated survival at 10 years in children: 87-93%

Severe clinical signs develop after 5-15 years: at long-term follow-up. IgAN in children is a progressive disease.