Bladder dysfunction (LUTD) in the pediatric recipient

Ann Raes
Pediatric Nephrology
11 januari 2017

Kids & grown ups are VERY different

<table>
<thead>
<tr>
<th>Indication</th>
<th>LD (%)</th>
<th>Non-ECDD (%)</th>
<th>ECCD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular disease</td>
<td>27.2</td>
<td>22.1</td>
<td>17.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.4</td>
<td>20.1</td>
<td>26.2</td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis</td>
<td>10.5</td>
<td>16.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Failed previous graft</td>
<td>3.7</td>
<td>13.4</td>
<td>6.3</td>
</tr>
</tbody>
</table>

LD, living donor; ECDD, extended criteria deceased donor.

Yearly incidence rate – 6-8/million age-related population

Obstructive uropathy
Dysplasia
VUR
Renal transplant evaluation & outcomes

Improved outcomes the past decade

- Better allograft procurement protocols/ living related donation
- Improved immunosuppression protocols
- Better preparation (notably with living related transplantation)
- Improved pre, peri and post op care
- Prevention and treatment of complications

https://web.emmes.com/study/ped/annrept/

LUTD in pediatric recipient is different based on underlying cause of ESRD

- Urological cause vs Nephrological cause

Unsuitable anatomy and function of bladder

Functional disorder
**CAKUT: Impact of LUTD on graft function?**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>LUTD patients</th>
<th>Urologic cause</th>
<th>Parameters reported</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warshaw et al.</td>
<td>1980</td>
<td>52</td>
<td>Complications, graft survival, patient survival</td>
<td>In pediatric patients with LUTD posttransplant renal recovery, with increased frequency</td>
<td></td>
</tr>
<tr>
<td>Renberg et al.</td>
<td>1988</td>
<td>18</td>
<td>Graft function, graft survival, patient survival</td>
<td>PUV adversely affects pediatric renal transplant function and survival</td>
<td></td>
</tr>
<tr>
<td>Churchill et al.</td>
<td>1988</td>
<td>18</td>
<td>Graft survival</td>
<td>Obstructive nephropathy, including PUV, has a negative effect on renal transplant survival</td>
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<tr>
<td>Squilliet et al.</td>
<td>1990</td>
<td>17</td>
<td>Complications</td>
<td>Prepubertal approach</td>
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<tr>
<td>Mochon et al.</td>
<td>1992</td>
<td>14</td>
<td>Complications</td>
<td>A history of PUV increases the incidence of posttransplant UTI</td>
<td></td>
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<tr>
<td>Solomon et al.</td>
<td>1997</td>
<td>66</td>
<td>Graft function, graft survival</td>
<td>Obstructive nephropathy</td>
<td></td>
</tr>
</tbody>
</table>

*Seven patients were transplanted into an ileal conduit.*
LUTD: Tailoring the pretransplant evaluation

- Congenital uropathy
- Neurogenic bladder
- Recurrent UTI
- LUT dysfunction
  - OAB, UAB, dysfunctional voiding
- Defunctionalized bladder

LUTD: Evaluation of the lower urinary tract

- Etiology of the renal failure
- History of lower urinary tract dysfunction
- Abdominal US
- VCUG
- Urodynamic studies
- Bladder diary (PVR)
- Uroflowmetry

According to the degree of LUTD
Bladder diary

**Overactive bladder/urge incontinence**

<table>
<thead>
<tr>
<th>Time</th>
<th>Drinks</th>
<th>Voided vol</th>
<th>Little</th>
<th>Activity</th>
<th>Urgency</th>
<th>No.</th>
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<tbody>
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<td>115</td>
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**Underactive bladder/voiding postponement**

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</table>

**MVV** = 270 ml
**MVV = 500 ml**
*(185 % MMV*$_{age}$*)

Uroflowmetry: non-invasive UDS

- **Uroflow:**
  - Potty-trained child
  - Bladder capacity
  - Emptying phase
  - At least 2 uroflows
  - Normal curve is “bell shaped”

- **Ultrasound:**
  - Post-voiding residual urine
  - Anatomy of the bladder
Uroflow/EMG Studies in 2 different 4 yr. old girls with LUTS and recurrent UTI. Both suspected of Dysfunctional Voiding (DV).

Study on left consistent with urgent voiding in child with confirmed DV. Study on right reflects straining to void in child with only mild urge to void, despite a voided volume 180% of her EBC. Two separate conditions with similar flow patterns showing the usefulness of including pelvic floor EMG.
Cystometry: Invasive UDS

Information:

- **Storage function**
  - Detrusor activity
  - Pressure
  - Compliance
  - Cystometric capacity

- **Voiding function**
  - Outflow obstruction
  - Flow pattern
  - Detrusor contractility
  - Sphincter activity/relaxation

- VCUG: anatomy/ VUR

Back to basics ....The normal urinary bladder

**Filling phase**
- **Bladder**: EBC: \[(\text{age} + 1) \times 30\] ml
  - Low pressure, Compliant
    - \(P_{\text{det}} < 30-40\) cm H\(_2\)O
  - **Urethra**: closure pressure must be > bladder pressure

**Voiding phase**
- \(P_{\text{det}} (P_{\text{ves}}-P_{\text{abd}}) = \pm 60\) cm H\(_2\)O
- Bladder: Coordinated detrusor contraction
- **Urethra**: Relaxation of the sphincter, pressure \(\leq 80\) cm H\(_2\)O
Louise, 13 yr

Bad bladder to transplant a kidney
The challenge: a safe bladder

- Adequate storage
  - Low-pressure
  - Good capacity reservoir
- Adequate emptying
  - Urinary drainage
- For all renal transplantation patients

Treatment options

- Conservative measures

  - Bladder training
    - ± pharmacologic agents
      - Anticholinergics, botox
      - Urinary prophylaxis
    - Clean intermittent catheterization (CIC)
  - Bladder cycling: controversy
    - Defunctionalized bladder
    - Anuric patients
Why is there need to intervene?

When the bladder is a bad bladder:
• High intravesical pressure
• Small capacity
• Low compliance
Not always easy to determine

When the whole or part of the continence system fails leading to incontinence, 'a social disease'
• Bad bladder
• Bad outlet
• Both
The abnormal bladder and transplantation

1971- (Tunner) Pediatric kidney transplants drained to urinary conduits.
1982- (Marshall) Augmentation cystoplasty following kidney transplant
1984- (Stephenson) Pediatric kidney transplants drained to augmented bladder

Treatment options

Bladder augmentation: ileocystoplasty
Catheterization of a Mitrofanoff channel
Do we have outcome data on graft function?

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>LUTD patients</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bums et al.</td>
<td>1992</td>
<td>4</td>
<td>Surgical treatment of lower urinary tract dysfunction is compatible with pediatric renal transplantation, permitting sterile voiding per urethra and a functioning bladder</td>
</tr>
<tr>
<td>Bures et al.</td>
<td>1994</td>
<td>9</td>
<td>Reconstruction of the lower urinary tract and transplantation is justifiable in patients with LUTD and ESRD</td>
</tr>
<tr>
<td>Norden et al.</td>
<td>1996</td>
<td>14 (median age 25 yr)</td>
<td>Results of renal transplantation in patients with surgically reconstructed lower urinary tracts are excellent</td>
</tr>
<tr>
<td>Nahas et al.</td>
<td>1997</td>
<td>14 (mean age 28 yr)</td>
<td>Graft survival after surgical reconstruction of lower urinary tract function in patients with dysfunctional bladders is excellent</td>
</tr>
<tr>
<td>Tanna et al.</td>
<td>1998</td>
<td>4</td>
<td>Patients &gt;18 yr</td>
</tr>
<tr>
<td>Power et al.</td>
<td>2000</td>
<td>10</td>
<td>Patients &gt;18 yr</td>
</tr>
<tr>
<td>Nahas et al.</td>
<td>2002</td>
<td>24 (mean age 27.5 yr)</td>
<td>Renal transplantation can be performed safely after augmentation cystoplasty</td>
</tr>
<tr>
<td>Zafarghandi and Ghobadi</td>
<td>2003</td>
<td>6</td>
<td>Mean age 21.6 yr</td>
</tr>
<tr>
<td>Defour et al.</td>
<td>2003</td>
<td>19</td>
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</tr>
<tr>
<td>Taghi et al.</td>
<td>2007</td>
<td>36 (median age 7.5 yr)</td>
<td>Bladder augmentation can be performed with an acceptable outcome in patients who have renal failure or who have undergone renal transplantation</td>
</tr>
</tbody>
</table>

*All ages stated are that at transplantation.

Complications

- **No significant difference in urologic complications (± 19%)**
  - Otukesh et al., Ped Transpl 2008
  - Lopez et al, Ped Transpl 2000

- **Urinary tract infections**
  - No significant differences (AC/CIC)
    - Traxel et al, J Urol 2011
  - More UTI in augmented group
    - Sager et al, Pediatr Surg Int, 2011
    - Lopez et al, Front pediat, 2013
  - No permanently impact on graft function

- **Malignancy**
  - No increase in risk of cancer over the inherent cancer risk
Suggested approach to the management of the pediatric patients with ESRD and LUTD

Close monitoring of LUTD after TX

Difference between nephrological and urological primary disease?

Table 2: Urodynamics and ultrasound findings in renal recipients, 5–26 years of age, with various underlying diseases.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cong UDM</th>
<th>Cong UFM</th>
<th>Acquired</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent bladder capacity</td>
<td>17/17 (100%)</td>
<td>17/17 (100%)</td>
<td>11/11 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Absent bladder tone</td>
<td>34/66 (51%)</td>
<td>12/22 (55%)</td>
<td>10/17 (59%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bilateral bladder tone</td>
<td>22/66 (34%)</td>
<td>8/22 (36%)</td>
<td>7/14 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Any bladder dyskinesis</td>
<td>40/66 (60%)</td>
<td>7/22 (32%)</td>
<td>7/14 (50%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. 1: Mean glomerular filtration rate (GFR) in renal recipients, 5–26 years of age, with and without bladder dysfunction (obstructed, non-obstructed) at discharge and 1 year after discharge.

Difference between nephrological and urological primary disease?

- Regardless of primary disease, transplanted children have high prevalence of LUTS (72%)
- Many had abnormal uroflowmetry (50%) and high PVR (32%)
- No direct link between LUTS and graft function
- Possible cause of LUTS: longlasting polyuria preceding transplantation.
- Recommends focus on bladder function regardless of primary disease.


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Difference between nephrological and urological primary disease?

<table>
<thead>
<tr>
<th>Table 1: Frequency uroflow chart</th>
<th>Nephrological Disease</th>
<th>Urological Disease</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts.</td>
<td>16</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>Max voided vol. (ml)</td>
<td>528</td>
<td>656</td>
<td>596</td>
</tr>
<tr>
<td>Range</td>
<td>350–600</td>
<td>300–600</td>
<td>300–800</td>
</tr>
<tr>
<td>Max voided rate (ml/s)</td>
<td>0.98</td>
<td>1.65</td>
<td>2.03</td>
</tr>
<tr>
<td>Range</td>
<td>1.02–1.220</td>
<td>1.89–2.516</td>
<td>1.22–1.529</td>
</tr>
<tr>
<td>Min. voided rate (ml/s)</td>
<td>1.81</td>
<td>1.51</td>
<td>2.05</td>
</tr>
<tr>
<td>Range</td>
<td>0.90–3.250</td>
<td>1.273–2.502</td>
<td>0.850–3.209</td>
</tr>
<tr>
<td>Max. residual (ml, p &lt; 0.05%)</td>
<td>2.8</td>
<td>6.2</td>
<td>5.82</td>
</tr>
<tr>
<td>Range</td>
<td>3–10</td>
<td>5–10</td>
<td>3–10</td>
</tr>
<tr>
<td>Normal Uroflow rate, 3 or fewer, or 9 or more (%)</td>
<td>8.030</td>
<td>3.16</td>
<td>0.260</td>
</tr>
</tbody>
</table>

Van der Weide et al, J Urol, 2006; 175:297-302

Van der Weide et al, J Urol, 2006; 175:297-302
Children w. nephrological disease have a high prevalence of LUTS (75%)

Predominant abnormality:
- High bladder capacity (75%)
- PVR (50%)
- UTI (43%)

No substantial difference in occurrence between 2 groups

Children w. nephrological disease should be examined for voiding dysfunction

LUTD in nephrological primary disease?

Significant negative correlation between Ccr and PVR urine volume (P =0.03) and UTI (P = 0.003)

Sensation of incomplete emptying was only marginally significant (may be due to VUR or dysfunctional voiding)

The presence of PVR urine increases the risk of developing UTI

PVR + UTI after renal transplantation may result in renal transplant deterioration.
UTI: important clinical problem (20-60%)

- Increased incidence of UTI after TX with a urological etiology
- No statistical difference among the various immunosuppression regimens

Silva et al, Ped urology, 2010, 1462-1467

UTI: impact on graft function?

- No correlation between UTI after RTX and poor graft outcome (median follow up 3.12 y)
- Aggressive treatment is mandatory
- Preventable measures

Silva et al, Ped urology, 2010, 1462-1467
Nocturnal symptoms (nocturia/enuresis)?

- Nocturia among transplanted children/adolescents: 53%
- Enuresis among transplanted children/adolescents: 28%
  - Van der Weide et al, J Urol, 2006; 175:297-302

- ABNORMAL DIURNAL RHYTHM OF URINE OUTPUT FOLLOWING RENAL TRANSPLANTATION – THE IMPACT OF BLOOD PRESSURE AND DIURETICS
  - K. Alstrup et al. Transplant Proc. 2010
  - N = 17 Recent transplant (Tx1, max 12 weeks)
  - N = 17 Late transplant (Tx2, max 12 months)
  - N = 17 Healthy control

- Sign. larger nocturnal diuresis in RTX

Nocturnal symptoms (nocturia/enuresis)?

- High prevalence of nocturia (74%), especially after 12 weeks
- Nocturnal polyuria associated with lack of nocturnal BP-dip and high fluid intake during daytime
- Tx. with diuretics reduces nocturnal polyuria, BP and nocturia
Conclusion

- Children with urological causes of ESRD can be successfully transplanted and outcomes are comparable with children without LUTD
  - Thorough assessment
  - Optimization of LUT
  - Approach tailored to individually patient

- Children with nephrological causes may develop LUTS
  - > UTI, PVR, nocturia
  - Close follow up after TX
  - Bladder rehabilitation