Top-down approach to the evaluation of urinary tract infections in children

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Vesicoureteral Reflux and the development of Pediatric Urology

The more that we looked for reflux the more often we found it. This was the real launching point for pediatric urology. Here we had a prospect of a surgical operation curing a common complaint ….

Sir David Innes Williams
BJU 2003
THE CROSS-ROADS OF UTI’s & VUR ...

IMAGING?

ANTIBIOTIC PROPHYLAXIS?

SURGICAL / ENDOSCOPIC TREATMENT?
Reflux Urinary Infections and Scarring

Intrarenal Reflux

and the

“Big Bang” theory

of Renal Scarring

Intrarenal Reflux
The “Big Bang”

... and Scarring
What role does VUR play in UTI?

- Sign
- Disease
- Risk factor

**VUR with dilatation increases**
- Risk of pyelonephritis
- Inflammatory reaction
- Risk of permanent renal damage
- Extent of renal damage
Reflux enhances inflammation

Swerkesson, Hansson et al. *JUrol* 2007

![Box plot showing CRP levels with p<0.01](image)

Renal scarring vs UTI

Jodal 1987
Renal scarring vs VUR

Grade of VUR

% Renal Scarring

Extent of renal damage versus VUR

Grade 0 - II
Grade III-V

Discrete  Mild  Moderate  Severe

Stokland et al. 1996
Assumption trap: apparent in practice patterns

Febrile UTI = Pyelonephritis

Pyelonephritis due to VUR (in absence of significant hydronephrosis)

Assumption trilogy

Febrile UTI = Pyelonephritis

Pyelonephritis due to VUR

Therefore…. febrile UTI = VUR
Acute pyelonephritis and VUR

94 children febrile UTI

62 (65.9%) DMSA +

12 (19.3%) VUR +

12 vs 94 (12.7%) 

Therefore, not all pyelonephritis due to VUR 

Majd, Rushton et al. J Peds 1991

DMSA in acute pyelonephritis and VUR

52 children febrile UTI

- > 5 years old
- Acute DMSA / US
- Early VCUG (5-7 days)

<table>
<thead>
<tr>
<th>Renal Unit</th>
<th>Normal DMSA</th>
<th>Abnormal DMSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VUR (+)</td>
<td>4 (28.5%)</td>
<td>10 (71.4%)</td>
</tr>
<tr>
<td>VUR (-)</td>
<td>25 (27.7%)</td>
<td>65 (72.2%)</td>
</tr>
</tbody>
</table>

Abnormal DMSA scan common with and without VUR

Ataei et al. Ped Nephro 2005
Winds of Change

- Genetic Studies
- Prenatal Diagnosis

Sibling reflux

- Identical twins 60 %
- Non identical twins 30 %
- Siblings 15 – 30 %
- General population 1 %
Genetic Factors

- Abnormal Kidneys
- The Reflux Itself?
- The susceptibility to Urinary infection?
- The susceptibility to scarring once reflux has occurred?

Reflux and Reflux nephropathy

*Male infants without UTI*

<table>
<thead>
<tr>
<th>Grades</th>
<th>Abnormal kidney</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades I - III</td>
<td>4 / 72</td>
<td>5.5 %</td>
</tr>
<tr>
<td>Grades IV</td>
<td>18 / 36</td>
<td>50.0 %</td>
</tr>
<tr>
<td>Grades V</td>
<td>34 / 42</td>
<td>80.9 %</td>
</tr>
</tbody>
</table>

Godley et al. *BJU* 2001
Vesico-Ureteric Reflux

- Most abnormal kidneys are congenital
- A minority are acquired scarring
- New scars are rare and getting rarer

Prenatal Diagnosis

- Approximately 15% of hydronephrosis
- Identifies males with bad kidneys
- Real sex ratio at birth unknown
The refluxing infants

<table>
<thead>
<tr>
<th>VUR resolved</th>
<th>Bladder normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 month</td>
<td>8 years</td>
</tr>
<tr>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td>50 %</td>
<td>50 %</td>
</tr>
<tr>
<td>0 %</td>
<td>33 %</td>
</tr>
</tbody>
</table>

Godley et al. *BJU* 2001

Great Ormond Street data

Normal bladder function
VUR resolved

Normal bladder function 50%
VUR resolved 50%

Normal bladder function 10%
VUR resolved 0%

Godley et al. *BJU* 2001
Infection

Genetic predisposition

A Field Defect
- Abnormal Kidney
- Abnormal Ureter
- Abnormal VUJ
- Abnormal Bladder
Abnormal Kidney

- “Normal”
- Mildly Abnormal
- Abnormal
- Seriously Dysplastic

Abnormal UVJ

- Highly Abnormal “golf hole”
- Lateral
- Diverticulum
- Short tunnel
- Marginally Abnormal……Potentially Refluxing
- “Normal” Non refluxing
Abnormal Bladder

A consequence of
- Trigonal Abnormality
- Reflux ` Residual`

Very variable expression

UTI Predisposition / Risk factors

Anatomic abnormalities
- Vesico-ureteral reflux
- Obstruction
- Diverticulum
- Other anatomic abnormalities

Female labial adhesions
Uncircumcised male

Constipation
Voiding dysfunction
Instrumentation
Sexual activity / pregnancy
Urinary infections - Pyelonephritis - Renal scarring

Host Biological Susceptibility

Anatomic Factors

Bacterial Virulence

Genetic predisposition to scarring?

- IRR
- Immune response

P fimbriated bacteria
GAG
Receptors
it is not about the uretero-vesical junction …

it is all about the KIDNEY!

Reflux management assumption …

Imaging

• Which children?
• When?
• How?
Ultrasound not helpful in evaluation of children with febrile UTIs.
In the context of a normal renal ultrasound examination, cystography contributes little to the management of children under the age of 1 year with a UTI.
### Imaging

**Recommended imaging schedule for infants**

**< 6 months**

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Atypical UTI</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DMSA 4–6 months following the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUH</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Imaging

**Recommended imaging schedule for infants and children**

**6 months and older but younger than 3 years**

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Atypical UTI</th>
<th>Recurrent UTI</th>
</tr>
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<td>Ultrasound within 6 weeks</td>
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<td>No</td>
<td>Yes</td>
</tr>
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<td>DMSA 4–6 months following the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUH</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
### Imaging

Recommended imaging schedule for children *3 years and older*

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Atypical UTI</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DMSA 4–6 months following the acute infection</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUG</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### When should we image?

In the **acute phase**
- Parents highly motivated
- Rapid identification of malformations
- No f-up in children with normal findings
- F-up by late DMSA scan in 50%

In the **late phase**
- Parents not so motivated
- Late identification of malformations
- F-up in all children necessary
- ‘double’ investigations can be avoided
Need a way to identify child at risk ...
Acute DMSA and UTI
VUR implications

Majd M., Rushton H.G., Jantausch B. et al
Relationship among VUR, P-fimbriated E.Coli and acute pyelonephritis in children with febrile urinary tract infection

*J Pediatr 119: 578, 1991*

Rosenberg A.R., Rossleigh M.A., Brydon M.P. et al
Evaluation of acute UTI in children by DMSA : a prospective study

*J Urol 148: 1746-1749, 1992*

Acute DMSA and UTI
VUR implications

65 children febrile UTI
- Acute DMSA and ultrasound
  - VCUG
  - 6 month DMSA
- + Acute DMSA → 57 %
- + Late DMSA → 11 %
- + VCUG → 24 %
  - 10/11 + DMSA
  - 1/11 Hydronephrosis

US and DMSA identified all refluxers

*Rosenberg et al. J Urol 1992*
Frequency of abnormal “acute” DMSA in case of clinical pyelonephritis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majd</td>
<td>1991</td>
<td>66%</td>
</tr>
<tr>
<td>Rosenberg</td>
<td>1992</td>
<td>57%</td>
</tr>
<tr>
<td>Melis</td>
<td>1992</td>
<td>62%</td>
</tr>
<tr>
<td>Jakobsson</td>
<td>1992</td>
<td>78%</td>
</tr>
<tr>
<td>Benador</td>
<td>1994</td>
<td>67%</td>
</tr>
<tr>
<td>Levtchenko</td>
<td>2000</td>
<td>68%</td>
</tr>
<tr>
<td>Hoberman</td>
<td>2000</td>
<td>61%</td>
</tr>
<tr>
<td>Benador</td>
<td>2001</td>
<td>65%</td>
</tr>
</tbody>
</table>

mean = 65.5%

Risk of late sequelae in case of abnormal “acute” DMSA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levchendo</td>
<td>2000</td>
<td>&lt; 2 years</td>
<td>15</td>
</tr>
<tr>
<td>Hoberman</td>
<td>2000</td>
<td>1 mo – 15 years</td>
<td>32</td>
</tr>
<tr>
<td>Benador</td>
<td>2001</td>
<td>1 year</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 1 year</td>
<td>33</td>
</tr>
</tbody>
</table>

normal = sequelae @ 6/12 in 0%
abnormal = sequelae @ 6/12 in up to 30%

early selection of a group at risk
What if?

**US and VCUG**
- Standard evaluation for UTI in children

**US and Acute DMSA**
- Reserve VCUG for positive DMSA
303 children < 2 yrs febrile UTI

- DMSA/VCUG acutely and 1 – 2 yrs
  51.5 % (+) acute DMSA (156/303)
  48.5 % (-) acute DMSA (147/303)

- 26.4 % VUR (80/303)
  66.2 % (+) acute DMSA (53/80)
  33.8 % (-) acute DMSA (27/80)

Acute DMSA vs VUR

<table>
<thead>
<tr>
<th>DMSA</th>
<th>No VUR</th>
<th>I° – II°</th>
<th>III° – IV°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>120</td>
<td>20</td>
<td>7*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.3 %</td>
</tr>
<tr>
<td>Positive</td>
<td>103</td>
<td>24</td>
<td>29</td>
</tr>
</tbody>
</table>

* 6/7 normal late DMSA (1 duplex with scarring)
5/7 VUR resolved
0/7 Recurrent UTI’s

Hansson, Jodal  
*J Urol* 2004
Follow-up prospective study

**290 children** fully evaluated

significant VUR would have been missed only in 1 child based on a normal renal scan ....

by screening children first with a DMSA scan and performing VCUG only in those with renal changes

140 of 290 patients (48%) would not have undergone cystograms .....

---

**Varese**

**June 2000 – October 2006**

177 patients age: 1mo - 13 years (median 13mo)

**Inclusion criteria**
- Fever > 38.5°C
- Leucocytosis
- Positive urine colture
- ESR & CRP elevated

**Exclusion criteria**
- Pelvic dilatation > 12 mm
- Ureteric dilatation > 6 mm
- Lithiasis

**Methods**

**Within 5-7 days from admission**
- Renal/Bladder US + DMSA-A

**1 month after APN**
- Cystography
  - MCU for males and DCS for females

**> 6 months after APN**
- Control DMSA scan
  - only DMSA-A + and/or RVU +

---

**Normal DMSA - A**

<table>
<thead>
<tr>
<th>L.P.O.</th>
<th>POST</th>
<th>R.P.O.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Acute pyelonephritis

POST R.P.O. POST

L Acute pyelonephritis: resolution

DMSA-A

Control (6/12)

L.P.O POST
L Acute pyelonephritis: scarring

DMSA-A

Control (6/12)

L.P.O  POST

Number of children: 177

Males  31.6 %  56
Females  68.4 %  121
Age at UTI

Sex distribution related to DMSA
Sex distribution related to DCS/MCU

VUR vs acute DMSA

<table>
<thead>
<tr>
<th>DMSA</th>
<th>No VUR</th>
<th>I° – II°</th>
<th>III° – IV°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>72 (40.6%)</td>
<td>5</td>
<td><strong>4.5 %</strong></td>
</tr>
<tr>
<td>Positive</td>
<td>62 (35.0%)</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>134 (75.7%)</td>
<td>24</td>
<td>19</td>
</tr>
</tbody>
</table>
## VUR vs acute DMSA

<table>
<thead>
<tr>
<th>DMSA</th>
<th>No VUR</th>
<th>I° – II°</th>
<th>III° – IV°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>72 (40.6 %)</td>
<td>5 4.5 %</td>
<td>3</td>
</tr>
<tr>
<td>Positive</td>
<td>62 (35.0 %)</td>
<td>19 19.8 %</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>134 (75.7 %)</td>
<td>24 24.3 %</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VUR</th>
<th>Negative DMSA</th>
<th>Positive DMSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>♂</td>
<td>♀</td>
</tr>
<tr>
<td>Absence</td>
<td>72</td>
<td>62</td>
</tr>
<tr>
<td>I°</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>II°</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>III°</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>IV°</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>V°</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### F-up: VUR + DMSA -

<table>
<thead>
<tr>
<th>DMSA</th>
<th>DCS / ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Normal</td>
<td>1 Persistent (III°)</td>
</tr>
<tr>
<td>5 Not Performed</td>
<td>3 Spont. Resol.</td>
</tr>
<tr>
<td></td>
<td>4 Not performed</td>
</tr>
</tbody>
</table>

8 pts

### F-up: VUR + DMSA +

<table>
<thead>
<tr>
<th>DMSA</th>
<th>DCS / ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 Abnormal</td>
<td>10 Persistent</td>
</tr>
<tr>
<td></td>
<td>3 Surgery</td>
</tr>
<tr>
<td></td>
<td>7 Deflux</td>
</tr>
<tr>
<td></td>
<td>8 Spont. Resol.</td>
</tr>
<tr>
<td></td>
<td>5 Downgrading</td>
</tr>
<tr>
<td></td>
<td>Stop proph.</td>
</tr>
<tr>
<td>10 Normal</td>
<td>2 Persistent</td>
</tr>
<tr>
<td>2 Not performed</td>
<td>2 Deflux</td>
</tr>
<tr>
<td></td>
<td>5 Spont. Resol.</td>
</tr>
<tr>
<td></td>
<td>3 Downgrading</td>
</tr>
<tr>
<td></td>
<td>Stop proph.</td>
</tr>
</tbody>
</table>

35 pts
F-up : VUR - DMSA +
46 pts

<table>
<thead>
<tr>
<th>DMSA</th>
<th>DCS / ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Abnormal</td>
<td></td>
</tr>
<tr>
<td>36 Normal</td>
<td></td>
</tr>
<tr>
<td>3 Not performed</td>
<td></td>
</tr>
</tbody>
</table>

Overall permanent scarring : **30/177 (16.9%)**
With VUR → 23 (13.0%)
Without VUR → 7 (3.9%)
CONCLUSION
DMSA and VCUG

Should A-DMSA replace VCUG?

VCUG only if DMSA positive hydro / dilated ureter

Will miss < 10% VUR
Mostly low grade
Normal kidneys
Few UTI recurrences / scarring

What will be your “new” approach?

Bottom-up?
- MCU
- US

Top down?
- US
- Acute DMSA
- Selective MCU
Alternative options based on high risk group (positive A-DMSA)

- Treatment of APN tailored on DMSA
- Chemoprophylaxis in case of abnormal DMSA
- Stop follow-up in case of normal DMSA

Only ongoing prospective evidence-based studies will determine the optimal and minimal imaging of a child with acute UTI and the best management of children with VUR.

Reflux management of the future - 1

Target VUR patients at low risk for renal scarring / breakthrough UTIs

- Neonatal refluxers with normal kidneys
- Children at low risk for UTIs
  - Circumcised male with normal kidneys
  - Children with normal voiding patterns and normal kidneys
- Post toilet trained low grade refluxers
Reflux management of the future - 2

Target VUR patients at risk for renal damage

- Renal parenchymal changes
  - Dysplasia
  - Scarring
- Abnormal bladder function
  - Dysfunctional voiders
  - Neuropathic bladder
- Breakthrough upper UTIs
- Genetic predisposition to UTIs / renal scarring

High Risk Refluxers

Aggressively treat!

- Antibiotic prophylaxis
- Endoscopic correction
- Open reimplantation
“Maxima puerorum reverentia debetur”

Martialis

Maximum respect to the child is due!

Thank you!