Current Concepts and Controversies in the Imaging Evaluation of Children with UTI

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Work-up of UTI in Children: A Challenging Task

• Different imaging algorithms are used to evaluate children with UTI

• Numerous studies in pediatric, urologic, radiologic and nuclear medicine literature in past 20 years—often with conflicting data and conclusions
Different Diagnostic Protocols for Investigation of a First Febrile UTI in a Young Child

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>VCU G</th>
<th>DMSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAP 1999</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kass 2000</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hoberman 2003</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hansson 2004</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Royal Childr Hosp</td>
<td>+</td>
<td>&lt;6 mos</td>
<td>-</td>
</tr>
<tr>
<td>Melbourne</td>
<td></td>
<td></td>
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<tr>
<td>Cincinnati Childr</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
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<td>Westwood 2005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NICE 2007</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
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*From Montini et al. Pediatrics 2009*

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Guidelines for Imaging Work-up of UTI in Children

AAP Subcommittee on UTI
  Recommends VCUUG and US
  States that the role of DMSA is unclear

*Pediatrics 1999* *(In process of revision)*

NICE Guidelines (National Institute for Health and Clinical Excellence)
  Complex—multiple guidelines for various combinations of US, DMSA and VCUUG depending on patient age, patient response to therapy and if offending bacteria is typical (E.coli) or atypical.

*August 2007*
WARNING!! You may leave this session more confused than you were when you entered this session!!!!

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Imaging Modalities

Commonly used:

- Renal sonography
- Cystography (radiographic or nuclear)
- DMSA renal scan

Less commonly used:

- MRI
- CT
Is US an important study in the work-up of UTI?

Best study for hydronephrosis/hydrourerter (H/H):
- UPJ obstruction
- UVJ obstruction
- Posterior urethral valve
- Complicated duplications
- High grade VUR

H/H typically detected on prenatal sonography—
No need for US if prenatal study is normal

US is indicated in UTI evaluation—H/H, duplex collecting system
(Huang. Urology 2008)

US in the diagnosis of acute pyelonephritis—low sensitivity (74%) and specificity (57%)
(Majd. Radiology 2001)
DMSA Cortical Scintigraphy in the Diagnosis of Acute Pyelonephritis—Piglet Models

87% sensitivity and 100% specificity

*Rushton et al. J Urol 1988*

92% sensitivity and 94% specificity--equivalent to CECT and gad MRI

*Majd et al. Radiology 2001*
Radionuclide Cystography and VCUG in Reflux Imaging

RNC
- Extremely sensitive for diagnosing VUR-continuous imaging
- Much less radiation
- Less resolution
  - Inability to evaluate urethra
  - Less accurate grading of VUR

VCUG
- Sensitive for diagnosing VUR-intermittent imaging
- Higher radiation
- Excellent resolution
  - Able to evaluate urethra
  - Very accurate grading of VUR

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Imaging in UTI

General Agreement:
Main goal is to identify those kidneys at risk for acute pyelonephritis and scarring

Major Disagreements:
What studies? When? How?
Risk Factors for Acute Pyelonephritis and Scarring

Host factors:

- Vesicoureteral reflux (VUR)
- Obstruction

Bacterial virulence factors
What we know about VUR

• Most common abnormality seen in patients with UTI

• Prevalence ranges from 25% to 40% in various studies

• Most lower grades will spontaneously resolve over time
Traditional Beliefs about VUR in UTI

It is important to know if VUR exists because its presence is directly related to acute pyelonephritis, renal scarring and its sequelae, as well as recurrent UTI.

Once VUR is identified:
- Antibiotic prophylaxis to prevent recurrent UTI
- F/U cystogram 12 – 18 mos
- If no spontaneous resolution--Deflux or ureteral reimplantation.
Traditional Evaluation: Focus on VUR—"Bottom Up" Approach

Child with UTI

US CYSTOGRAM

VUR no VUR

DMSA No DMSA

Prophylaxis No prophylaxis

F/U cystogram 12-18 mos

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94 children with febrile UTI

66% with acute pyelonephritis on DMSA
37% with VUR

63% *without* demonstrable VUR
Acute Pyelonephritis occurring in the Absence of VUR

<table>
<thead>
<tr>
<th>STUDY</th>
<th>% Pts with APN and NO VUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majd 1991</td>
<td>63</td>
</tr>
<tr>
<td>Ditchfield 1994</td>
<td>61</td>
</tr>
<tr>
<td>Hansson 2004</td>
<td>66</td>
</tr>
<tr>
<td>Moorthy 2005</td>
<td>50</td>
</tr>
<tr>
<td>Preda 2007</td>
<td>70</td>
</tr>
<tr>
<td>Tseng 2007</td>
<td>63</td>
</tr>
</tbody>
</table>

So if focus only on the patients with VUR, will miss the majority of patients with APN
6 month old girl with febrile UTI; DMSA and VCUG done within 5 wks.

Acute pyelo LUP

No VUR

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Is VUR predictive of APN?

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majd 1991</td>
<td>37</td>
</tr>
<tr>
<td>Rosenberg 1992</td>
<td>40</td>
</tr>
<tr>
<td>Jacobsson 1994</td>
<td>34</td>
</tr>
<tr>
<td>Stokland 1996</td>
<td>47</td>
</tr>
<tr>
<td>Benador 1997</td>
<td>38</td>
</tr>
<tr>
<td>Hansson 2004</td>
<td>34</td>
</tr>
<tr>
<td>Ataei 2005</td>
<td>13</td>
</tr>
<tr>
<td>Tseng 2007</td>
<td>30</td>
</tr>
<tr>
<td>Preda 2007</td>
<td>30</td>
</tr>
<tr>
<td><strong>AVERAGE</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

Slide courtesy of L. Binkovitz

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14 mos old girl with febrile UTI; DMSA and nuclear cystogram done within 3 weeks

Moderate LT VUR

Acute pyelo LUP

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2 yr girl with febrile UTI: DMSA and VCUG done within 4 wks

Bilateral grade III VUR

Normal DMSA
Acute Pyelonephritis and VUR in Renal Scar Formation

Rushton and Majd. J Urol 1992:
Initial and follow-up DMSA scans on 33 pts with APN

Prevalence of scarring: 42%
  40% with VUR
  43% without VUR

All new scars formed at the exact site of the acute pyelonephritic lesions

**Conclusion:** Acute pyelonephritis--the prerequisite for renal scar formation
## Acute Pyelonephritis and VUR in Renal Scar Formation

<table>
<thead>
<tr>
<th>Study</th>
<th>Scar Rate (%) in pts without VUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rushton 1992</td>
<td>43 (4-42 mos f/u)</td>
</tr>
<tr>
<td>Jakobsson 1994</td>
<td>62 (2 yr f/u)</td>
</tr>
<tr>
<td>Stokland 1996</td>
<td>53 (1 yr f/u)</td>
</tr>
<tr>
<td>Moorthy 2005</td>
<td>50 (3-6 mos f/u)</td>
</tr>
<tr>
<td>Garin 2006</td>
<td>46 (1 yr f/u)</td>
</tr>
<tr>
<td>Montini 2009</td>
<td>51 (1 yr f/u)</td>
</tr>
<tr>
<td>Siomou 2009</td>
<td>60 (6 mos f/u)</td>
</tr>
</tbody>
</table>

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Shift in Focus

Most patients with acute pyelonephritis do not have demonstrable VUR.

Acute pyelonephritis appears to be a more important risk factor than VUR for scar formation.

Focus is changing from the presence of VUR to the status of the kidney—acute pyelonephritis or scar.
Evolving Evaluation: Focus on Kidney Status—"Top Down" Approach

Child with Febrile UTI

DMSA

APN/scar
Cystogram

NL
No Cystogram

Central photopenia

No cystogram
US

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Does the Presence of VUR Matter at all?

High grades of VUR are associated with higher rates of renal scarring

*Jakobsson. Arch Dis Child 1994*
*Stokland. J Pediatrics 1996*

Can DMSA identify most patients with higher grades of VUR?

No consensus on “High grade VUR”:
> grade III by some authors and
> grade IV by other authors
Identification of Dilating VUR with DMSA

Pts with Abnormal DMSA who have Dilating VUR

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majd 1991</td>
<td>21/21</td>
<td>100</td>
</tr>
<tr>
<td>Rosenberg 1992</td>
<td>10/11</td>
<td>91</td>
</tr>
<tr>
<td>Jakobsson 1994</td>
<td>14/15</td>
<td>93</td>
</tr>
<tr>
<td>Stokland 1996</td>
<td>19/25</td>
<td>76</td>
</tr>
<tr>
<td>Hansson 2004</td>
<td>29/36</td>
<td>81</td>
</tr>
<tr>
<td>Ataei 2005</td>
<td>3/3</td>
<td>100</td>
</tr>
<tr>
<td>Moorthy 2005</td>
<td>1/1</td>
<td>100</td>
</tr>
<tr>
<td>Tseng 2007</td>
<td>21/21</td>
<td>100</td>
</tr>
<tr>
<td>Preda 2007</td>
<td>26/27</td>
<td>96</td>
</tr>
</tbody>
</table>

TOTAL 144/160 90%
Hansson et al. J Urol 2004
303 patients, retrospective study

27/80 with VUR had normal DMSA
  20/27 were grades I & 2
  7/27 were grades III-V: none of these 7 pts had scar on f/u DMSA

Conclusion: DMSA can replace VCUG for identification of kidneys at risk for APN and scar

290 children, prospective study

8/52 with VUR had normal DMSA
  7/8 with grade I-II
  1/8 with grade III-V—repeat DMSA at 2 yrs was normal

Conclusion: using DMSA as the first study, a significant number of VCUG exams can be avoided

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Top-Down Approach

Therefore, using DMSA as the first study in evaluation of a child with UTI, most of the cases of high grades of VUR, considered to be a risk factor in scarring, will be detected.

Also this approach will decrease the number of cystograms performed.
How does the “Top-Down” Approach affect Management?

Traditionally, only those patients with VUR were placed on prophylaxis.

With a decrease in the number of cystograms performed, fewer patients will be placed on prophylaxis.
Antimicrobial Prophylaxis for VUR

Prophylaxis maintains the urine infection-free and gives time for the VUR to spontaneously resolve.

Questions:
- Does prophylaxis truly decrease the rate of recurrent UTI?
- Does prophylaxis result in a decrease in the rate of renal scarring?
Does prophylaxis decrease rate of recurrent UTI?

Garin et al. Pediatrics 2006

218 patients with UTI (3 mos to 18 yrs) randomized to prophylaxis vs placebo for 1 yr—with or without VUR (only grades I-III VUR were included)

Rate of recurrent UTI (cystitis and AP):

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/VUR</td>
<td>23.6%</td>
<td>22.4%</td>
</tr>
<tr>
<td>w/o VUR</td>
<td>8.8%</td>
<td>23.3%</td>
</tr>
</tbody>
</table>

(p=0.06) (p=0.99)
Does prophylaxis decrease rate of renal scarring?

Garin et al. Pediatrics 2006
13/218 (5.9%) developed scars

Rate of renal scars

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/ VUR</td>
<td>9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>w/o VUR</td>
<td>4.5%</td>
<td>6.6%</td>
</tr>
<tr>
<td></td>
<td>(p=0.99)</td>
<td>(p=0.99)</td>
</tr>
</tbody>
</table>

Conclusions:
Lower grades of VUR (I-III) did not increase the incidence of UTI and did not result in increase in renal scarring.

Prophylaxis did not decrease the rate of recurrent UTI nor did it decrease the rate of renal scarring.
Does prophylaxis decrease rate of recurrent UTI?


- 4 centers
- 576 children (age 0-18 yrs) with UTI with or w/o VUR (all grades)
- Randomly assigned to prophylaxis or placebo for 12 months

Conclusions:
Prophylaxis decreased rate of recurrent UTI as compared to placebo, regardless of presence of VUR.
Typically recurrent UTI in the prophylaxis group were due to resistant bacteria.
The Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) Study
Keren et al. Pediatrics 2008

• Double-blind, randomized, placebo-controlled trial.

• 600 children with VUR to be enrolled, age 2 mos to 6 yrs

• Initial DMSA, US and VCUG on all patients.

• Randomized to receive placebo or trimethoprim/sulfamethoxazole for 2 years

• F/U DMSA at 1 and 2 years post infection

• F/U VCUG at 2 years post infection
The Randomized Intervention for Children With Vescicoureteral Reflux (RIVUR) Study
Keren et al. Pediatrics 2008

Primary outcome: recurrence of UTI

Secondary outcomes
1. time to recurrent UTI
2. renal scarring (assessed by DMSA scan)
3. treatment failure
4. development of antimicrobial resistance in stool flora
So…Who should receive prophylaxis?

Patients with VUR and a normal DMSA

Or

Patients with positive DMSA and no VUR

Pending results of the RIVUR Study
In the words of the True Pediatric GU Guru Massoud Majd, 18 years ago:

“Currently, the indication for low-dose antibiotic prophylaxis in infants and children with UTI is usually based solely on the presence of VUR regardless of its severity.

Perhaps direct scintigraphic evidence of parenchymal involvement at the time of acute symptomatic UTI is a more important determinant of the need for prophylaxis.

*A child with a positive DMSA scan, regardless of the status of reflux, may be a more reasonable candidate than a child with low-grade reflux and a normal DMSA scan."

In Summary

Evolving changes are occurring in the diagnostic work-up of children with UTI

Focus is shifting from emphasis on VUR to emphasis on the status of the kidney—acute pyelonephritis and scar on DMSA—“Top Down Approach”

Role of prophylaxis and role of VUR in renal scarring yet to be determined (RIVUR Study)