Overview

1. When does imaging help with a child presenting with a urinary tract infection?
2. Update our understanding of the pathogenesis of pediatric urinary tract infections.
4. What is on the horizon?
Febrile UTI in Children

- 60% of children with a febrile UTI have DMSA abnormalities
- Historically, 10-40% will have permanent renal scarring
- Older, retrospective studies have suggested a higher rate of chronic kidney disease, hypertension, and pre-eclampsia
- Prospective studies are limited, but suggest much lower rates of hypertension and diminished renal function

Renal Ultrasound

VCUG
16 day old male with fever, fussiness, and decreased po intake

Initial Renal Ultrasound → Antibiotic Therapy → 10 day follow up
## SFU Grading of Hydronephrosis

<table>
<thead>
<tr>
<th>SFU Grade</th>
<th>Pattern of Renal Sinus Splitting</th>
<th>IVP Appearance</th>
<th>Ultrasound Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Intrarenal Pelvis and Major Calyces</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pelvis, Major and Minor Calyces with Parenchymal Preservation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Grade 3 Dilation and Parenchymal Loss</td>
<td></td>
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</tbody>
</table>
# Urinary Tract Dilation Classification (UTD)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
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<tbody>
<tr>
<td>AP Renal Pelvic Diameter</td>
<td>&lt; 10 mm</td>
<td>&lt;15 mm</td>
<td></td>
<td>&gt; 15 mm</td>
</tr>
<tr>
<td>Calyceal Dilation</td>
<td>None</td>
<td>Central</td>
<td>Central and Peripheral</td>
<td>Central and Peripheral</td>
</tr>
<tr>
<td>Renal Parenchymal Thickness</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Thinned</td>
</tr>
<tr>
<td>Renal Parenchymal Appearance</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal echogenicity/cysts</td>
</tr>
<tr>
<td>Bladder Abnormalities</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Bladder wall thickening</td>
</tr>
<tr>
<td>Ureteral Abnormalities</td>
<td>Normal</td>
<td>Normal</td>
<td>Dilation</td>
<td>Dilation</td>
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</tbody>
</table>

- Grading is based on the most severe finding
- Antenatal classification also part of this classification

Acute Pyelonephritis

# Acute Pyelonephritis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT DMSA</td>
<td>92.1</td>
<td>93.8</td>
</tr>
<tr>
<td>CT</td>
<td>86.8</td>
<td>87.5</td>
</tr>
<tr>
<td>MRI</td>
<td>89.5</td>
<td>87.5</td>
</tr>
<tr>
<td>Power D US</td>
<td>74.3</td>
<td>56.7</td>
</tr>
</tbody>
</table>

DMSA uptake reflects renal tubular cell function and is affected by both intrarenal blood flow and proximal tubular cell membrane transport.

Gold standard for detection of acute pyelonephritis and renal scarring

97% agreement between DMSA and histopathology.

Radiation dose for 1 year old infant estimated at 0.7-1.0 mSv.
Renal DMSA

- Positive findings include segmental defects and significant functional discrepancy.
- Not generally useful for detection of hydronephrosis, vesicoureteral reflux, or renal abcess.
- Renal hypodysplasia or prior pathology can result in false positives.
Renal Hypoplasia and Dysplasia

- Renal hypoplasia - Morphologically normal kidney, with nephrons reduced in either number or size.

- Renal dysplasia - Kidney with disorganized renal parenchyma resulting from a failure to undergo normal cellular differentiation during organogenesis.

- Because the dysplastic features may be microscopic and the dysplastic tissue may be located as islets among normal tissue, renal dysplasia often is impossible to differentiate from renal hypoplasia or infectious scars through imaging alone.

Voiding Cystourethrography

Grading of Vesicoureteral Reflux (International Reflux Study)

Prevalence of Vesicoureteral Reflux

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>I</td>
<td>7%</td>
<td>4.8%</td>
</tr>
<tr>
<td>II</td>
<td>22%</td>
<td>23.6%</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>7.7%</td>
</tr>
<tr>
<td>IV</td>
<td>1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>V</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Chand (2003, also Cincinnati) Retrospective review of 15,504 patients < 7 years presenting after UTI with VUR. Overall estimated incidence of 39% for patients 1-24 months of age
Prevalence of Vesicoureteral Reflux as a function of the midpoint of each age stratum, as reported by Chand et al.
Voiding Cystourethrography

**Pros**

- Gold standard for detection of vesicoureteral reflux
- Excellent anatomic depiction of the urethra and bladder; also collecting systems and ureters if VUR present
- Reasonably inexpensive and available

**Cons**

- False Negatives - Cyclic technique in young children may show intermittent VUR in 25%
- Precise relationship between VUR and APN not fully understood
- Grid-controlled variable-rate pulsed fluoroscopy with last image hold substantially lowers dose as compared to CFL (approximately 1/10th; equivalent to 9 days of background radiation)

Radioisotope Cystogram

- Ability to continuously monitor for VUR
- Limited resolution
- Limited ability to detect lower grades and characterize the degree of reflux
- Dose approximately = 1 day of background radiation

Contrast-enhanced Voiding Urosonography

Indications:
- Females with 1st time VUR evaluation
- Follow-up VUR
- Screening high risk patients

Advantages:
- No ionizing radiation
- Greater sensitivity for VUR

Disadvantages:
- Cannot monitor all areas continuously
- No urethral depiction

Does Vesicoureteral Reflux even matter?
Childhood Urinary Tract Infections as a Cause of Chronic Kidney Disease

- Literature search identified 1,576 cases of chronic kidney disease
- “Vesicoureteral reflux with UTI - *without other structural abnormalities in the kidneys* - seems not to cause CKD”
- “In large *prospective* follow-up studies, the renal function of patients with *isolated* VUR has been well preserved.”
- “Active treatment of vesicoureteral reflux seems not to reduce the occurrence of CKD”

Vesicoureteral reflux: An accurate predictor of acute pyelonephritis in childhood urinary tract infection?

Prospective design

- 150 patients, 300 kidneys, age 0-5 years with first proven UTI

All underwent VCUG & DMSA/gluconate within 15 days

- 72/300 (24%) had a positive VCUG
- 88/300 (29%) had a positive DMSA
- 61% (54/88) had a negative VCUG

The ability of the VCUG to predict a DMSA defect;

- Sensitivity of 38.6% and specificity of 82.1%
- PPV 47.2% and NPV 76.3%

Ditchfield et al., Radiology (1994) vol. 190 (2) pp. 413-5
Retrospective
- 427 patients presenting with first febrile UTI
- Underwent RUS, VCUG, and acute phase DMSA
Divided into 2 groups:
- Normal RUS (354)
- Abnormal RUS (73)
DMSA findings were correlated with VCUG
Outcome measures:
- Recurrent UTI
- Change in management as a result of VCUG
- Outcome at discharge

Investigating febrile UTI in infants: Is a cystogram necessary?

354 infants with normal US

38 with scar on DMSA 11%
21 with VUR 55%

17 without VUR 45%

315 without scar on DMSA 89%

48 with VUR 15%

268 without VUR 85%
Investigating febrile UTI in infants: Is a cystogram necessary?

73 infants with abnormal US

43 with scar on DMSA 59%

23 with VUR 53%

20 without VUR 47%

30 without scar on DMSA 41%

22 with VUR 73%

8 without VUR 27%

Investigating febrile UTI in infants: Is a cystogram necessary?

Recommendations:

• All infantile febrile UTIs should have RUS and DMSA
• Where RUS is normal, VCUG should be performed in those with DMSA findings
• When RUS is abnormal, VCUG should be performed regardless of DMSA findings

The role of vesicoureteral reflux in acute renal cortical scintigraphic lesion and ultimate scar formation.

Graph demonstrates rate of acute photon defects and ultimate scar formation according to VUR grade.

389 patients with first febrile UTI

What is the Utility of Antimicrobial Prophylaxis?

- Prophylaxis does not reduce the rate of febrile UTI recurrence during 12 months after the first episode of febrile UTI in children with or without the presence of primary non-severe reflux.


- Continuous antibiotic prophylaxis is not effective in reducing the rate of infection and the incidence of renal damage and its progression.

Multiple other randomized trials examined the relationship between the effectiveness of antibiotic prophylaxis in different patient populations.

- (Roussey-Kesler et al., 2008) Another study of 225 randomized patients 1 month to 3 years of age with Grade I-III reflux showed no benefit of prophylaxis.

- (Garin et al., 2006) Another prospective randomized study of 218 children aged 3 months to 18 years of age suggests that grade I-III reflux does not increase the incidence of UTI / pyelonephritis, and that antibiotic prophylaxis does not appear to prevent the recurrence of UTI nor the development of renal scarring.

- (Conway et al., 2007) A retrospective review conducted from an electronic medical record suggested that recurrent UTIs were associated with high-grade (IV, V) reflux, Caucasian race, and ages 3-5; and that antibiotic prophylaxis was associated with increasing resistance of organisms.
Current Recommendations for Imaging in Pediatric UTI
Action Statement 5

Febrile infants with UTIs should undergo renal and bladder ultrasonography (RBUS)

- The yield of actionable findings is relatively low.
- The purpose of RBUS is to detect anatomic abnormalities that require further evaluation.
- RBUS also provides an evaluation of the renal parenchyma and an assessment of renal size.
- Widespread application of prenatal ultrasonography clearly has reduced the prevalence of previously unsuspected obstructive uropathy in infants.
American Academy of Pediatrics Clinical Practice Guideline
Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months

Action Statement 6a
VCUG should not be performed routinely after the first febrile UTI. Only when RBUS reveals;
- Hydronephrosis
- Scarring
- Other findings that would suggest either high-grade VUR or obstructive uropathy.

Action Statement 6b
Further evaluation should be conducted if there is a recurrence of febrile UTI.
- Benefits: VCUG after a second UTI should identify infants with very high-grade reflux.
- Harms/risks/costs: VCUG is an uncomfortable, costly procedure that involves radiation, including to the ovaries of girls.
- Role of patient preferences: As mentioned previously, the judgment of parents may come into play, because VCUG is an uncomfortable procedure involving radiation exposure.

Renal Scintigraphy
- The findings on nuclear scans rarely affect acute clinical management and are not recommended as part of routine evaluation of infants with their first febrile UTI.
## Diagnostic Algorithms for Urinary Tract Infection

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Ultrasound</th>
<th>VCUG</th>
<th>Acute DMSA</th>
<th>Late DMSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top Down Approach</td>
<td>No</td>
<td>For positive acute DMSA</td>
<td>Yes</td>
<td>For positive acute DMSA</td>
</tr>
<tr>
<td>NICE &lt; 6 mo</td>
<td>Yes</td>
<td>If positive US or atypical UTI</td>
<td>No</td>
<td>For atypical UTI</td>
</tr>
<tr>
<td>NICE &gt; 6 mo</td>
<td>For atypical UTI</td>
<td>For positive risk factors</td>
<td>No</td>
<td>For atypical UTI</td>
</tr>
<tr>
<td>Italian Society of Pediatr Nephrol</td>
<td>Yes</td>
<td>For positive US or risk factors</td>
<td>No</td>
<td>For positive US or VUR</td>
</tr>
<tr>
<td>American Academy of Pediatrics</td>
<td>Yes</td>
<td>For positive US</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Melbourne Royal Children’s Hospital</td>
<td>Yes</td>
<td>If boys &lt; 6 months or positive US</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Diagnostic Algorithms for Urinary Tract Infection

Utilized data from the Italian Renal Infection Study 1 (IRIS1) -

Multi-center, prospective, controlled trial involving 502 children, 304 of whom completed the diagnostic workup:

- Initial renal ultrasound (€82)
- Acute phase DMSA (€84; est. dose 1 mSv; within 10 d of UTI dx)
- VCUG within 2 months (€83; est. dose 1 mSv)
- DMSA @ 12 months for those with positive acute DMSA

Assessed detection of VUR, renal scars, radiation, and costs

# Diagnostic Algorithms for Urinary Tract Infection - Summary

## Top Down Approach
- Greatest sensitivity for renal scars and VUR
- Highest radiation
- Highest cost

## NICE and AAP
- Highest specificities for VUR

## ISPN
- Highest specificity for renal scars

## NICE
- Lowest cost

## AAP
- Lowest radiation

Pediatric Urinary Tract Infection: Future Trends & Opportunities

- Continued Prospective Studies
- Cost Benefit Analyses
- Inflammatory Markers
- Treatment
- Imaging
Urinary Tract Infections

- Inflammatory markers
  - Fever
    - Associated with increased likelihood of renal pathology
    - Greater risk of renal scarring
    - Sensitivity 53-84%; specificity 44-92%
  - White blood cell count
  - C-Reactive Protein
  - Procalcitonin
  - Urine heparin binding protein

Procalcitonin: Receiver Operating Characteristics

A  Acute Pyelonephritis  B  Renal Scars

Imaging Trends in Pediatric UTI

- Ultrasound
  - Harmonic Imaging
  - Microbubble Contrast
  - Elastography

- MRI
  - Image Acquisition/Motion Correction
  - Diffusion
  - Contrast Agents
Summary

- Past and current imaging approach for febrile UTI
- Urinary tract infection pathogenesis and the role of VUR
- Ultrasound UTD Classification for hydronephrosis
- Current AAP imaging guidelines for UTI
- Discussed potential developments with inflammatory markers, imaging, and treatment
Thank you!