Update on UTI guidelines

Evidence Based Medicine for the Management of Urinary Tract Infections in Febrile Infants 2-24 Months Old

Robert Ettenger, MD
Professor of Pediatrics
Mattel Children’s Hospital UCLA

DISCLOSURE

I have no financial relationships with commercial interests

Format

- Short Clinical Vignettes
- Questions About Diagnosis Treatment, Short and Long Term Management
- There Is No Wrong Answer
- A Brief Examination of Current Concepts and Ideas That May Influence Practice Patterns
- 2011 AAP Guideline Recommendations and Action Points will be highlighted
- No Financial Disclosures
Objective of this Talk

- Understand how to utilize diagnostic criteria to diagnose and treat urinary tract infections in febrile children 2-24 months old
- Apply evidence-based recommendations for diagnostic imaging in febrile infants and young children with a urinary tract infection
- Implement into clinical practice evidence-based guidelines for ordering a voiding cystourethrogram in children 2 to 24 months with a history of a febrile urinary tract infection.

Based on the AAP Clinical Practice Guidelines

Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2-24 Months of Age

This is not meant to be the sole source of guidance, but rather to assist physicians in decision-making. These do not replace clinical judgment.

Designations of Evidence Quality

<table>
<thead>
<tr>
<th>Evidence Quality</th>
<th>Dependence of Benefit or Harm</th>
<th>Balance of Benefit and Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Option</td>
<td>No Rec</td>
</tr>
<tr>
<td>Moderate</td>
<td>Partial Option</td>
<td>Partial Balance of Harm</td>
</tr>
<tr>
<td>Low</td>
<td>No Option</td>
<td>Reciprocal Balance of Harm</td>
</tr>
</tbody>
</table>

Figure 1: AAP evidence strength.
Renal parenchymal infection (pyelonephritis) can have clinically important sequelae in children.

Cystitis does not

High fever strongly suggests pyelonephritis

Often difficult, particularly in young children, to distinguish clinically between cystitis and pyelonephritis.

A 21 month old Caucasian girl comes to your office with intermittent fever to 101.5°F x 4 days, mild irritability and occasional vomiting.

No localizing sign for cause of fever.

You would like to start the child on antibiotics because she appears ill.

Not dehydrated.

Parents are reliable.

The overall prevalence of UTI is approximately 5% of febrile illnesses, but varies by race and sex.

Prevalence in White >> Black by 2-4 fold

Prevalence in Females >> Circ. Males 2-4 fold

Caucasian Females with Temp > 39° C have a prevalence of UTI of 16%
If a clinician decides that a febrile infant with no apparent source for the fever requires antimicrobial therapy to be administered because of ill appearance or another pressing reason, the clinician should ensure that a urine specimen is obtained for both culture and urinalysis before an antimicrobial agent is administered; the specimen needs to be obtained through catheterization or SPA.
AAP 2011 Action Statement 2

- If a clinician assesses a febrile infant with no apparent source for the fever as not being so ill as to require immediate antimicrobial therapy, then the clinician should assess the likelihood of UTI.

UTI: Concepts that May Influence Practice Patterns

- The overall prevalence of UTI is approximately 5% of febrile illnesses, but varies by race and sex.
- Prevalence in White >> Black by 2-4 fold.
- Prevalence in Females >> Circ. Males 2-4 fold.
- Caucasian Females with Temp > 39° C have a prevalence of UTI of 16%.

WHAT IS YOUR NEXT STEP?

1. Send a urinalysis and start antibiotics for UTI as outpatient if > 10 WBC / HPF.
2. Bag the child for a urine culture, and when urine is obtained, begin antibiotics, and adjust antibiotics according to sensitivity results.
4. Catheterize for urine culture, and then begin immediate treatment with antibiotics.
5. Admit to hospital, obtain catheterization culture, start antibiotics and fluids.
UTI: Concepts that May Influence Practice Patterns


- White
- Fever > 39° C
- Fever for > 2 days
- No other source of fever
- Females < 4 years
- Males < 12 months
- Uncirc. Male
- Dysfunctional Elimination and/or constipation
- Vesicoureteral Reflux
- Obstruction
- History of UTI
- Sexual Activity
- Malodorous urine
- Hematuria
- Abdominal or suprapubic tenderness
- Appears "Sick"
- Bacterial-Host Interactions
  - alteration of periurethral flora
- Bacterial Structures to engage host receptors

AAP 2011 Action Statement 2a Evidence Quality A: Strong Recommendation

- When a clinician determines that the infant has a low likelihood of UTI, then clinical follow-up monitoring without specific UTI testing is sufficient
AAP 2011 Action Statement 2b

IF THE PHYSICIAN DETERMINES THAT A PATIENT IS NOT IN A LOW RISK GROUP, THEN 2 CHOICES:

CHOICE 1 – Obtain urine for
- Culture by SPA or Catheterization
- Urinalysis

CHOICE 2
- Obtain urine by most convenient method and send for urinalysis
- If UA Suggests UTI, obtain urine by SPA or Catheterization, send for culture
- If UA of fresh urine is negative for leukocyte esterase and nitrite, monitor clinical course
- Recognize that a negative UA cannot rule out UTI with total certainty

What About the “Bag” for culturing the urine??

1. A high false-positive rate: a positive culture of urine collected in a bag is likely to be a false positive result 80% of the time
2. The sensitivity of a bag urine culture is 100%, no false negative tests usually and a negative culture rules out a UTI

But a positive culture must be corroborated by a culture using SPA or catheterization

Culture obtained by catheterization for culture has a sensitivity of 95% and a specificity of 99%

Observations About Urinary Diagnostic Tests for UTI

- Dipstick may miss as much as 12% (LE + Nitrile sensitivity 88%), so culture is still necessary in almost all cases
- A positive culture (anything > 50,000/ml) but without LE + or WBC on microscopic suggests asymptomatic bacteriuria and:
  - Is not the cause of a high fever
  - Should not be treated with antibiotics
  - The proposed criteria for infection includes both a positive culture and pyuria.
- It takes 4 hours in bladder for nitrite to be generated by bacteria, so this test is specific, but only 50% sensitive, and particularly problematic in young child. It is also present only in infections with Gram negative entheric organisms
- A child with neither pyuria nor bacteriuria is 17 times less likely to have a UTI than a child with either of these findings
- A child with both pyuria and bacteriuria is 85 times more likely to have a UTI than if tests were negative
- WBC Clumps are very suggestive of a UTI
Diagnostic Tests


<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>Leukocyte esterase test</td>
<td>83-94</td>
<td>84</td>
</tr>
<tr>
<td>Nitrite test</td>
<td>15-82</td>
<td>54</td>
</tr>
<tr>
<td>Blood assessment</td>
<td>50-84</td>
<td>60</td>
</tr>
<tr>
<td>Protein assessment</td>
<td>40-50</td>
<td>30</td>
</tr>
<tr>
<td>Microscopic pyuria</td>
<td>53</td>
<td>75</td>
</tr>
<tr>
<td>Microscopic bacteria</td>
<td>16-90</td>
<td>88</td>
</tr>
<tr>
<td>Leukocyte esterase or nitrite test</td>
<td>80-100</td>
<td>80</td>
</tr>
<tr>
<td>Any positive test results in urinalysis</td>
<td>90-100</td>
<td>100</td>
</tr>
</tbody>
</table>

AAP Guidelines 2011: Action Statement 3: To Establish a Diagnosis of UTI: Evidence Quality C Recommendation

**Required**
- A urinalysis that suggests infection
  - Pyuria and/or
  - Bacteriuria
- The presence of at least 50,000 CFU/ml of a uropathogen cultured from a urine obtained by Catheterization or SPA

You Have Established that the Patient has Pyuria and An Organism Growing in Culture at >50,000 CFU/ml

**What is your next step in clinical management**
- 1. Do not treat with antibiotics yet – (await antibiotic sensitivities)
- 2. Identify local antimicrobial sensitivities and treat with a likely agent using IV therapy in hospital
- 3. Utilizing Home Health Agency and local antimicrobial sensitivities, initiate treatment with home IV therapy
- 4. Give one IM dose of Cephtriaxone and Initiate oral amoxicillin therapy
- 5. Initiate PO antibiotics with Amoxicillin-Clavulanate, Trimethoprim-Sulfamethoxazole, or Cephalexin
**AAP 2012 Action Statement 4a**

*Evidence Quality A: Strong Recommendation*

- Initiating treatment either orally or parenterally is equally effective
- Clinician should base choice of antibiotic on local antimicrobial sensitivities
- Clinician should subsequently adjust choice according to sensitivity testing of the isolated uropathogen

---

**UTI: CONCEPTS THAT MAY INFLUENCE PRACTICE PATTERNS**

1. Treatment prior to 72 hours effective to ↓ subsequent renal damage
2. In children <24 months, rates of symptomatic resolution, reinfection, and renal scarring did not differ between those treated orally and those treated IV [Randomized clinical trial]
3. Admit those who can’t tolerate oral medications (e.g. vomiting), or not responding to therapy or cannot be adequately followed
4. Mean time to defervesence is 24 hours

---

**Useful Oral Antibiotics to Begin Treatment Until Sensitivities Available**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>25–40 mg/kg per d in 3 doses</td>
</tr>
<tr>
<td>Suspenzine</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim sulphamethoxazole</td>
<td>6–12 mg/kg trimethoprim and 30–60 mg/kg sulphamethoxazole per d in 2 doses</td>
</tr>
<tr>
<td>Cefixime</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>50 mg/kg per d in 1 dose</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>20–30 mg/kg per d in 2 doses</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>50–100 mg/kg per d in 4 doses</td>
</tr>
</tbody>
</table>
Empiric Parenteral Antibiotics
Consider for Initial Treatment Until Sensitivities Are Available

An antibiotic course has been chosen
The patient is afebrile at 12 hours after beginning treatment

- 1. For 3 days beyond the day of defervesence
- 2. 5 days since this is likely only cystitis
- 3. 7 days
- 4. 10 days
- 5. 14 days

Please Designate Your Answer on the ARS
AAP 2012 Action Statement 4b
(Evidence Quality B: Recommendation)

- The clinician should choose 7 to 14 days as the duration of antimicrobial therapy in an attempt to prevent infection from becoming systemic and to prevent renal scarring.
- A Short Course (1-3 days) is associated with inferior outcomes.

Which of the following imaging strategies would you perform?
- None
- Renal and Bladder Ultrasound (UTZ)
- Voiding Cystourethrogram
- Both UTZ and VCUG
- DMSA scan

Please Designate Your Answer on the ARS
AAP 2012 Action Statement 5
(Evidence Quality C: Recommendation)

- Febrile infants with a [first] UTI should undergo a renal and bladder (RB) ultrasound (UTZ)
  - To detect anatomic abnormalities that require further evaluation
  - RBUTZ should be performed in the first 2 days of treatment if the patient when the clinical illness is unusually severe or patient is not recovering promptly
  - If there is substantial clinical improvement RBUTZ can (and probably should be) deferred because of possibility of confounding findings
    - Endotoxin from E. coli can produce dilatation during acute infection and confused with hydronephrosis
    - Changes in size, shape, and echogenicity from edema during acute infection

When is a routine VCUG appropriate to perform in this case?

- 1. After first febrile UTI
- 2. If RBUTZ reveals hydronephrosis or renal scarring
- 3. If RBUTZ suggests high grade vesiculo-ureteral reflux (VUR) or obstructive uropathy
- 4. If there is a recurrence of a second febrile UTI
- 5. If there is any atypical or complex clinical circumstances

Please Designate Your Answer on the ARS
AAP 2012 Action Statement 6a
(Evidence Quality B: Recommendation)
- VCUG should not be performed routinely after a first febrile UTI
  - There is insufficient to continue to recommend this!
- VCUG indicated if RBUTZ indicates
  - Hydronephrosis
  - Renal Scarring
  - Other findings suggesting high grade VUR or obstruction
- VCUG also indicated if there are other atypical or complex clinical circumstances

AAP 2012 Action Statement 6b
(Evidence Quality X Recommendation)
- Further evaluation should be conducted if there is a recurrence of a febrile UTI (i.e., a second or subsequent UTI)

**Reflux Classification**

- **International Reflux Classification**
  - Color indicates the degree of reflux up the ureter and the calyces (i.e., the area where urine collects in the kidney).
  - **Ureter only**
  - **Pelvocalyceal system**
  - **Pelvocalyceal Dilatation**
  - **Scallop, Blunting, ureteral dilatation**
  - ** Massive dilatation of calyceal system and ureter, + intrarenal reflux**
The patient has been treated successfully, but experiences a second UTI 2 months after the first. A VCUG is performed. Grade III reflux is demonstrated.

- Which of the following courses would you follow:
  1. No treatment; Close observation. When patient has a febrile illness, have parents bring patient promptly to MD for urinalysis and culture.
  2. Prophylactic antibiotics x 1 year. Repeat VCUG at end of that year and if VUR resolved, S/C antibiotics.
  3. Surgical reimplantation of the ureters.
  4. Endoscopic sub-ureteral injection of tissue-augmenting substance.
  5. Continuous antimicrobial prophylaxis without repeat VCUG.

Medical Management of VUR

**Previous Mainstream View**

- Mainstream View: Suppressive antibiotics
  - Continue until VCUG shows no reflux
  - 30% incidence of breakthrough UTI
  - Improve voiding dysfunction if possible.
  - New Study suggests that less frequent VCUG (Thompson et al Pediatr 2005)
    - Every 2 years with mild VUR
    - Every 3 years with moderate to severe VUR.
**Do We Need Prophylaxis?**

- The committee formulating the guidelines requested that the authors of the most influential RCTs send the *raw data* from these RCTs for reanalysis.
- They performed a rigorous analysis of all of the data to assure that their recommendations were truly evidence based.
- They performed a chi square testing and meta-analysis utilizing this data.

---

**There was no detectable statistically significant benefit of prophylaxis with Grades I - IV**

<table>
<thead>
<tr>
<th>Reflux Grade</th>
<th>Prophylaxis</th>
<th>No of Recurrences</th>
<th>Total N</th>
<th>No of Recurrences</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7</td>
<td>210</td>
<td>10</td>
<td>103</td>
<td>85</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>57</td>
<td>2</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>155</td>
<td>11</td>
<td>124</td>
<td>124</td>
</tr>
<tr>
<td>III</td>
<td>31</td>
<td>140</td>
<td>40</td>
<td>145</td>
<td>189</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>55</td>
<td>20</td>
<td>49</td>
<td>79</td>
</tr>
</tbody>
</table>

---

**AAP 2012 Action Statement 7** *(evidence quality: C; Recommendation)*

- After confirmation of UTI, the clinician should instruct parents or guardians to seek prompt medical evaluation (ideally within 48 hours) for future febrile illnesses, to ensure that recurrent infections can be detected promptly.
Conclusions

- Determine if child needs immediate antimicrobial therapy
- Diagnosis is based on the presence of pyuria and at least 50,000 CFUs per ml of a single uropathogen in an appropriately collected sample.
- RBUS should be performed to detect anatomic abnormalities
- Routine VCUG after the first UTI is not recommended
- VCUG should be performed if there is recurrence of febrile UTI