Updates in Guidelines for Febrile UTI in Infants and Young Children

Andi Marmor, MD
December, 2012

Objectives
- Recognize infants who should be tested for UTI
- Choose the best method of collecting urine in a febrile infant
- Interpret the results of a UA/urine culture
- Apply newest recommendations for imaging after first febrile UTI in your practice

Background: Febrile UTI
- Most common bacterial infection in infants <24 months with fever without a source (FWS)
- Diagnostic challenge!
- Pyelonephritis (upper tract) common
  - Bacteremia/urosepsis in young infants
- May herald presence of UT abnormalities
  - Predispose to recurrent UTI, kidney damage
- 2011 AAP Guidelines were long-awaited...

2011 AAP Guidelines: Methods
- Committee on QI and Management
  - Gen pediatrics, epi, ID, nephrology, radiology, urology
  - No financial conflicts of interest
  - Reviewed by multiple groups
- 2 searches of literature over the last 10 years
- Systematic review on prophylactic abx
  - Authors contacted to provide raw data
1. Who should be tested for UTI?
2. How should urine be obtained for testing?
3. How should we make the diagnosis?
4. How should we treat UTI in young children?
5. When is imaging needed?

Background: Dilemmas

Updated in 2011 AAP Guidelines

Case Presentation

- Bruno is a 5 month old boy who has “felt hot” at home for 3 days, vomited once this morning
- Temp 39.1 in clinic, remaining VS are normal
- Non-toxic and only mildly dehydrated
- No source for fever found on history or PE
- PMH: generally healthy, has received 3 doses of PCV-13. Uncircumcised
- Question 1: Should we test him for UTI?
Summary of What’s New: Diagnosis

1999 GUIDELINE
- Collect urine in all girls and uncircumcised boys <2 + circ boys <1 with FWS
- Various thresholds for + culture (10-100K)

2011 GUIDELINE
- Use clinical factors to decide if risk of UTI is >1-2%
- +UA and + culture (>50 K) necessary for dx of UTI

AAP Action Statements: Urine Collection

1. In infant requires abx, get cath urine (A)
2. If abx not required, assess likelihood of UTI (A)
   a. If low*, observation OK
   b. If not low, then obtain urine (cath or bag)

*“low” = < 2%?

AAP Table of Probabilities of UTI in Febrile Infants

Table: Probability of UTI Among Febrile Infant Girls and Infant Boys According to Number of Findings Present. *Probability of UTI exceeds 1% even with no risk factors other than being uncircumcised.

- Girls with FWS and 2 other risk factors have risk > 2%
- All uncircumcised boys with FWS have risk >2%
- Circumcised boys with FWS and all 3 risk factors have risk > 2%

1. In infant requires abx, get cath urine (A)
2. If abx not required, assess likelihood of UTI (A)
   a. If low*, observation OK
   b. If not low, then obtain urine (cath or bag)
Prior Probabilities of UTI in FWS:
Age, Gender and Circumcision:
- Infants <3 months of age:
  - Overall risk is 10-15%
  - Uncirc boys highest risk group
  - Bacteremia in 15-20%
- Infants and children >3 months of age:
  - Girls 3-24 mo ~10%
  - Uncirc boys 3-6 mo: 5-10%->2% by 1 year
  - Circ boys <1%
- Low/moderate baseline probabilities should be modified based on other risk factors!

"Other Risk Factors?"
- Height of fever
- Duration of fever
- Ethnicity?
  - Girls: white
  - Boys: non-black
    - Latino boys at higher risk, even when controlled for circumcision status

Marmor Recs: Which infants with FWS should be tested for UTI?
- I think that ~ 5% is a reasonable threshold, unless infant is at high risk for severe illness
- <3 months of age (T>38)
  - All infants
- 3-24 months of age (T>39)
  - Girls: with fever for ≥ 2 days
  - Boys:
    - Uncircumcised <6 months of age (< 12 if other risk fx)
    - Circ boys: consider only if other risk factors present

Back to our case...
- What is Bruno’s approximate risk of UTI?
  - Based on age (5 mo), circumcision status (uncircumcised) and duration of fever (3 days): best estimate ~5-10%
- You decide to test for UTI
- Question 2: How do you want to collect Bruno’s urine?
How Do You Want to Collect Bruno’s Urine?

A. Urethral catheter  
B. Supra-pubic bladder aspiration  
C. Clean catch  
D. Diaper pad

Action Statements: Urine Collection

1. In infant requiring abx, get cath urine (A)  
2. If abx not required, assess likelihood of UTI (A)  
a. If low, observation OK  
b. If not low, then obtain urine (cath or bag)*

*AAP Recs: bag OK for UA, but if +, cath for culture

Urine Collection Options

Suprapubic aspiration (SPA)  
Catheter  
Urine bag  
Surprise “clean catch”
Suprapubic aspiration (SPA)  
Catheter  
Urine bag  
Surprise “clean catch”

Specificity of LE lower in bag  
62-84% vs 91-94% for cath  
But sensitivity is similar  
This makes a negative bag UA more helpful than a positive one  
Especially in a low-risk pt...

Since the culture is our “gold standard” we need to minimize false positives AND false negatives  
False POSITIVES with bag culture  
Depend on the gender, technique, and + threshold  
False NEGATIVES  
Depend on the threshold chosen for positive test...  
Higher threshold = ↓false pos, ↑false negs

Since the culture is our “gold standard” we need to minimize false positives AND false negatives  
False POSITIVES with bag culture  
Depend on the gender, technique, and + threshold  
False NEGATIVES  
Depend on the threshold chosen for positive test...  
Higher threshold = ↓false pos, ↑false negs  
Usual + threshold is >100,000 orgs  
Rate of FP and FN both ~15% at this threshold
Predictive value of bag culture

- Does bag culture (using 100,000K threshold) change PP enough to be useful?

<table>
<thead>
<tr>
<th>Prior Prob</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>23%</td>
<td>1%</td>
</tr>
<tr>
<td>10%</td>
<td>40%</td>
<td>2%</td>
</tr>
<tr>
<td>20%</td>
<td>60%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Prior Prob PPV NPV

- 5% 23% 1%
- 10% 40% 2%
- 20% 60% 4%

The best use of the bag culture is to rule OUT UTI in the low prior probability patient.

Practical Application

- High Risk
  - Infant < 6 mo of age
  - Systemically ill
  - Further workup if +UTI
  - Cath urine preferred
    - Treat if +
- Low/Mod Risk
  - > 6 mo of age
  - Well-appearing
  - First time UTI
  - Bag urine OK
    - Good NPV
    - If UA+, consider sending cath specimen for culture

Case Continued

- Since Bruno is uncircumcised, <6 mo of age, and he has had a high fever for several days, you decide to get a cath urine.
- The UA is positive for LE.
- Question 3: What would you do next?
AAP Action Statements: Diagnosis

1. In infant requiring abx, get cath urine (A)
2. If abx not required, assess likelihood of UTI (A)
   a. If low, observation OK
   b. If not low, then obtain urine (cath or bag)
3. Diagnosis requires + UA and + culture of at least 50K of a uropathogen (C)

Committee on QI and Management
Gen peds, epi,, ID, nephrology, radiology, urology
No financial conflicts of interest
Reviewed by multiple groups
2 searches of literature over the last 10 years
Systematic review on prophylactic abx
Authors contacted to provide raw data

2 assumptions:
1. Low sensitivity of LE is due to false + cultures
   • False negatives occur in pts with asymptomatic bacteriuria
   • True sensitivity is higher, so infection unlikely if LE negative
2. Diagnosing infants with asymptomatic bacteriuria as having UTI does more harm than good
   • The number of true UTI’s missed will be small
   • Benefits of not over-treating > risk of missing a UTI

Where did this recommendation come from?

2 assumptions:
1. Low sensitivity of LE is due to false + cultures
   • False negatives occur in pts with asymptomatic bacteriuria
   • True sensitivity is higher, so infection unlikely if LE negative
2. Diagnosing infants with asymptomatic bacteriuria as having UTI does more harm than good
   • The number of true UTI’s missed will be small
   • Benefits of not over-treating > risk of missing a UTI

Both true in low-risk infants...
### Background: Dilemmas

1. Who should be tested for UTI?
2. How should urine be obtained for testing?
3. How should we make the diagnosis?
4. How should we treat UTI in young children?
5. When is imaging needed?

### Treatment of Febrile UTI

- Local microbiology/sensitivity should determine treatment
- PO antibiotics for 10 days for most infants
  - IV if ill-appearing, < 2 months of age, or poor PO
Case continued

- Bruno is treated with oral cephalexin for 10 days, and is afebrile after 24 hours
- His urine culture grows >100,000 colonies of E. Coli
- Question 4: Does he need imaging to exclude a urinary tract abnormality?

What Does the AAP Guideline Recommend for this Infant?

A. Renal ultrasound
B. Voiding cysto-urethrogram (VCUG)
C. Renal DMSA scan
D. No imaging

Summary of What's New: Imaging

1999 GUIDELINE
- Ultrasound:
  - Earliest convenience
  - Urgent if poor response
- VCUG:
  - Earliest convenient time
  - Prophylactic abx while awaiting VCUG

2011 GUIDELINE
- Ultrasound:
  - Earliest convenience
  - Urgent if poor response
- VCUG:
  - If abnormal ultrasound
  - After 2nd UTI
  - Antibiotics not recommended

Summary of What's New: Imaging

1999 GUIDELINE
- Ultrasound:
  - Earliest convenience
  - Urgent if poor response
- VCUG:
  - Earliest convenient time
  - Prophylactic abx while awaiting VCUG
  - Antibiotics not recommended

2011 GUIDELINE
- Ultrasound:
  - Earliest convenience
  - Urgent if poor response
- VCUG:
  - If abnormal ultrasound
  - After 2nd UTI
  - Antibiotics not recommended
Action Statements: Imaging

1. Febrile infants with UTI should have renal US (acutely if ill, or after resolution if well) – (C)
2. VCUG
   a. Should NOT be performed routinely (B)
   b. Consider if highly abn US or recurrent UTI (X)

Let’s take a step back....

- Goals of imaging after 1st UTI are to
  - Identify significant urinary tract abnormalities
  - Prevent recurrent UTI’s and further renal damage

Posterior Urethral Valve (PUV)

- Tissue remnant in the male urethra
  - 1 in 5-8,000 pregnancies
  - Majority identified prenatally
- Presentation in infancy:
  - Distension, poor urine stream, renal failure, urosepsis
  - 15-20% progress to ESRD despite surgical management
- Prognosis independent of UTI, age at presentation¹
- Damage already done?

What is Vesico-Ureteral Reflux (VUR)?

- Retrograde flow of urine during voiding
- Most common urinary tract abnormality
- ~30-50% of infants <3 years with 1st UTI
  - Most outgrown in childhood

¹DeFoor, 2008
Choice of Imaging: Ultrasound

- Inexpensive and relatively non-invasive
  - Operator-dependent
- Good for:
  - Obstruction, gross structural abnormalities
- What about VUR?
  - Specificity for VUR is high, but sensitivity low
  - Sensitivity for high-grade VUR ~85%
  - Good NPV in low-risk patients!

Choice of Imaging: VCUG

- More sensitive and specific
- More invasive, involves radiation
- Necessary? IF
  - VUR predicted recurrent UTI’s and progressive renal damage AND
  - Intervention were effective at preventing these consequences
Does VUR Cause Recurrent UTI?
- Recurrence rate similar between children with/without VUR
- UTI’s recur despite repair of VUR

VUR and Renal Scarring?
- Scarring more likely to be found in infants with hi-grade reflux AND recurrent UTI
- BUT
  - Scarring does not seem to be directly related to UTI recurrence or presence of VUR
  - Non-progressive, may occur without VUR and without UTI’s

Does VUR Cause Progression to ESRD?
- Incidence of ESRD = 5/million
- 5-12% of patients with ESRD have reflux nephropathy as a “cause”
- Risk of ESRD after episode of pyelo?
  - Craig: 1/10,000
  - Blumenthal: < 1/million
- Aggressive treatment of VUR in the last 30 years has not affected ESRD rates

Choice of Imaging: VCUG
- More sensitive and specific
- More invasive, involves radiation
- Necessary? IF
  - VUR predicted recurrent UTI’s and progressive renal damage AND
  - Intervention were effective at preventing these consequences
**Efficacy of VUR Management:**
- Retrospective: medical vs surgical management
  - No difference in scarring
  - Cochrane review (2004): medical vs medical + surgical
  - Rates of recurrent UTI and scarring similar
  - Need RCT of surgical vs expectant management!

**Efficacy of Prophylactic Antibiotics**
- Multiple RCT’s of kids with 1st time UTI, +/- VUR
  - None have shown significant difference between groups in UTI recurrence or renal scarring
  - Trend towards:
    - Recurrence and resistance MORE likely in those receiving antibiotics
    - More recurrences in those with higher grade VUR
  - Limitations:
    - Study sizes limited
    - Variable inclusion of children with high-grade reflux

**So...Does Finding VUR Help Kids?**
- Antibiotics do not seem to prevent recurrent UTI or renal scarring in kids with/without VUR
- Fixing VUR confers no additional benefit
- 2011 AAP Guideline:
  - “If [antibiotic] prophylaxis is, in fact, not beneficial...then the rationale for performing VCUG routinely after an initial febrile UTI must be questioned”

**Will we miss significant abnormalities with selective imaging strategies?**
- Schroeder, 2011
  - Retro review before/after new imaging policy
  - *NO change* in UTI recurrence, detection of high-grade VUR
  - *Decrease* in imaging, abx and low-grade VUR
- Pennesi, 2012
  - Retrospective review of 406 kids with 1st UTI
  - Only those with abnormal U/S got VCUG
  - Of the 7% who had abn US, 13% had scarring = 1.5% total
Action Statements: Imaging

1. Febrile infants with UTI should have renal US (acutely if ill, or after resolution if well) – (C)
2. VCUG
   a. Should NOT be performed routinely (B)
   b. Consider if highly abn US or recurrent UTI (X)

AAP Evidence Strengths

<table>
<thead>
<tr>
<th>Evidence Quality</th>
<th>Preponderance of Benefit or Harm</th>
<th>Balance of Benefit and Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Well designed RCTs or diagnostic studies on relevant population</td>
<td>Strong Recommendation</td>
<td>Strong Recommendation</td>
</tr>
<tr>
<td>B. RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies</td>
<td>Recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>C. Observational studies (case-control and cohort design)</td>
<td>Option</td>
<td>No Rec</td>
</tr>
<tr>
<td>D. Expert opinion, case reports, reasoning from first principles</td>
<td>Option</td>
<td>No Rec</td>
</tr>
<tr>
<td>X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm</td>
<td>No Rec</td>
<td>No Rec</td>
</tr>
</tbody>
</table>

What about DMSA?

- Nuclear isotope
- Documents renal scarring
- Most useful for research....
Marmor Recs: Imaging

- Goals: Find severe abnormalities that need to be treated or followed
- Ultrasound
  - After first infection if < 3 mo, recurrent if > 3 mo
  - In acute infection if unusual clinical course
- VCUG only if
  - UT obstruction/abnormality on ultrasound
  - Recurrent UTI + VUR on U/S and surgical correction considered

Summary of Recommendations: Who To Test

- Consider pyelonephritis in all infants <24 mo with FWS
- Test for UTI in when probability >5%, or concern is high
  - All infants <3 months of age with FWS (T>38)
  - 3-24 months of age (T>39)
    - Girls with fever for ≥ 2 days
    - Uncircumcised boys <6 mo (< 12mo if other risk fx)
    - Circ boys: ONLY if other risk factors present

Summary of Recommendations: Imaging

- Obtain ultrasound
  - In complicated or recurrent UTI
  - Consider after 1st UTI in high risk or very young infants
- Consider VCUG
  - If ultrasound shows high grade VUR or obstruction and surgical correction is considered
- Antibiotics are NOT recommended to prevent recurrent UTI's, even in patients with known or suspected VUR
  - Diagnose and treat recurrent febrile UTI in all infants!

What Does the AAP Guideline Recommend for this Infant?

A. Renal ultrasound
B. Voiding cysto-urethrogram (VCUG)
C. Renal DMSA scan
D. No imaging

My practice: no imaging, if he responds to treatment...
Thank you!