Urinary Tract Infections in Infants & Toddlers: An Evidence-based Approach

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No disclosures

- Biases
  - Errors of commission are worse than errors of omission
  - I don’t like urethral instrumentation
  - The history of urologic approaches to recurrent UTI in children should inspire humility and conservatism

Importance of Topic

- Possibility of UTI comes up in every febrile infant
- Diagnosis of UTI has significant cost and treatment implications
- 2007 NICE guideline and newer evidence
New guideline and studies

- NICE guideline, 2007
- 5 new RCT's of prophylactic antibiotics:
  - Montini et al, 2008
  - Craig et al, 2009
  - Brandstrom et al, 2010
- New data on natural history of UTI (Craig, 2010)
- New AAP Guideline, October 2011

Focus of this Talk

- Febrile infants
- No clear source for fever
- Age 2-3 mos to 2-3 years (not toilet trained)
- Two key decisions
  - Which infants should have urine tested?
  - What imaging studies should be done?
- More complete presentation--- see my website
  Google "Thomas B. Newman"
Pretest: Which of the following is the strongest predictor of UTI in febrile children < 24 months?
- A. African-American (vs. White) (OR~0.3)
- B. Fever > 39° (vs lower fever) (OR ~1.8)
- C. Being an uncircumcised boy (vs circumcised) (OR ~8)
- D. Having no apparent source for fever (OR ~2)
- E. Vomiting (OR ~1)

Decision #1: Which infants should have urine tested?
- Depends on
  - Prior probability of UTI
  - History and physical exam findings suggestive of UTI or other diagnoses
  - Costs of testing (including difficulty obtaining specimen)
  - Risks and benefits of treatment in those with and without UTI
Estimated prior probability of UTI in febrile infants*  
- Circumcised boy: 0.5-1%  
- Uncircumcised boy: 5-10%  
- Nonwhite girl: 3-5%  
- White girl: 5-15%  

*Sources: Hoberman et al, Pediatrics 1993; 91:1196  

Example Likelihood Ratios for Positive Urine Culture in Febrile Infants (<2 years)  
- Source for fever?  
  - Definite: .3  
  - Possible: .7  
  - No: 1.5  
- Height of fever?  
  - <39: .7  
  - 39-40: 1.4  
  - >40: 2.5  

*Sources: Hoberman, 1994; Kramer: 1993

Does This Child Have a Urinary Tract Infection?*  
- Systematic review of studies of UTI in children  
- Likelihood ratios for signs and symptoms presented  
  - Except for UA results, suprapubic tenderness and circumcision, most single findings of limited value  
  - T >39 for >48 h AND no source: LR = 4  
- Useful review but…  
  - Overly aggressive diagnostic algorithms proposed  

*Shaikh N et al. JAMA 2007;298:2895-2904
Does This Child Have a Urinary Tract Infection?*

- Algorithm for febrile girls & uncirc. boys
- Only 1 Risk factor needed!

*Shaikh N et al. JAMA 2007;298:2895-2904, figure 3

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Does This Child Have a Urinary Tract Infection?*

- Except in blacks, these authors recommend UA and UC for:
  - Girls and uncircumcised boys with any fever of any duration even if they look well and have an apparent source
  - Circumcised boys with any fever > 24 hours even if they look well and have an apparent source
- Seems like too low a threshold to me
  - Recommendations like these make people suspicious of "evidence-based medicine."

*Shaikh N et al. JAMA 2007;298:2895-2904, figures 2 & 3

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Benefits of Diagnosing UTI

- Treat current illness
  - Make patient feel better
  - Prevent worsening (development of bacteremia/sepsis)
- Prevent future sequelae
  - Identify patients who may benefit from imaging to detect underlying abnormalities
  - Identify patients who may benefit from prophylactic antibiotics
What happens if you miss a UTI?

- **PROS** Febrile infant study: 807 febrile infants <3 months old
  - no urine test first visit
  - not treated with antibiotics
  - 61 UTIs expected
  - Only two later diagnosed; both did fine
- **Conclusion:** even in this high-risk age group most UTIs resolve spontaneously


What happens if you miss a UTI?

- Prospective cohort study of 15,781 febrile illnesses in children < 5 years old
- 1140 cases of serious bacterial infection (UTI in 543, Pneumonia in 533, bacteremia in 64)
- 363/1140 (32%) not initially treated
  - 230 subsequently treated
  - Only 8 (1.4%) "unwell" at follow-up average of 10.2 days later, none febrile
  - Only death was in a child with terminal illness

*Craig J et al. BMJ 2010;340:c1594

Patients most likely to benefit from early UTI diagnosis

- Younger patients (<6 months and especially < 3 months)
- Sicker patients (higher fever, more irritable)
- Patients who have been sick longer
- Patients with evidence of underlying disease, e.g., recurrent fevers of uncertain origin, poor growth, poor urine flow, antenatal renal abnormality
- Patients for whom follow-up is difficult
Recommendation #1: Obtain a urine sample when level of concern about UTI is high, e.g.:
- Child appears acutely ill without source
- Illness lasting > 2-3 days or recurrent unexplained fevers
- Age < 3 mos
- Underlying disease or difficult follow-up
- Significant risk of UTI (10%)
  - Girls, no source T>39
  - Boys 3-12 months if uncircumcised
- Include parents in the decision if culturally appropriate

Decision #2: Imaging after UTI
- What are you looking for?
- How much cost and risk is it worth to find it?

After a first uncomplicated febrile UTI in a 15 month old girl with no other indications, would you recommend a VCUG
A. Always
B. Almost always
C. Usually
D. Sometimes
E. Rarely
F. Never
Abnormalities on Urinary Tract Imaging

- Obstruction -- treatable
- Vesicoureteral reflux --- questionable benefit of treatment
- Duplications of collecting system – no management change
- Scarring- little or no management change

Renal Ultrasound

- Safe, noninvasive, no radiation
- Can identify significant obstructive lesions
- May miss duplications, reflux
- Low yield (obstruction or change in management 0/309*), especially with normal 3rd trimester ultrasound
- Charges (UCSF, 2010) $1214

*Hoberman et al., NEJM 2003

99Tc-DMSA Scan

- Measures (relative) function
- Abnormal acutely in pyelonephritis
- Relatively noninvasive
- “Scarring” in ~10%, but rarely changes management
- Charges (2010, UCSF) $1813 without SPECT, $4856 with SPECT
VCUG or RNC

- Involves urethral catheterization to fill bladder
  - Uncomfortable, frightening, risk of introducing infection
- Only way reliably to identify VU reflux
- RNC lower radiation dose, but lower resolution and can’t see urethra
- Used to be widely recommended
- Charges (UCSF 2008) $1306
  - ($280 Pharmacy charge for contrast!)

Rationale for Treatment of VU Reflux

- Reflux + Infection → Scarring
- Scarring → HTN, Preeclampsia, Chronic Kidney Disease, ESRD
- Prevent sequelae by fixing reflux (surgery/Deflux®) or preventing infection (prophylactic antibiotics)
- Inconsistent evidence to support this rationale

Meta-analysis of prophylactic antibiotics to prevent UTI: 1. Effect on UTI

- Also: Brandstrom (2010): RR= 0.39 (95% CI: 0.2, 0.75) for febrile UTI (P=0.003), NNT ~4 x 2 years**
- NNT in Craig study = 17 x 1 year

**Brandstrom et al. J Urol 2010;184:286-91
Meta-analysis of prophylactic antibiotics to prevent UTI: 2. Effect on scarring*

- Craig et al, 2009: HR for infection 0.6 but no effect on scarring, RR 0.83 (0.28, 2.5)
- Brandstrom et al, 2010: New renal damage on DMSA scan 0% vs 13% (P=0.003); NNT= 8


Value of VCUG to determine whether to give prophylactic antibiotics is bounded by:

- Benefit of treating someone with VU reflux
  - Small or nonexistent for infections, uncertain for scarring
- Harm of treating someone without reflux
  - Small to nonexistent, since recurrent UTI can be prevented in these children

NICE Imaging Recommendations, < 6 months

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Asympt. UTI</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during acute infection</td>
<td>No</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>Yes*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DMSA 6-8 months following acute infection</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MCU</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* See box for definitions.
** If asymptomatic consider MCU

NICE Imaging Recommendations, 6 months to 3 years

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute UTI</th>
<th>Atypical UTI</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during acute infection</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DUSG 4-6 months following the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUG</td>
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<td>Yes</td>
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</tr>
</tbody>
</table>

*See box for definitions.

NICE definitions of atypical and recurrent UTI

- Atypical UTI
  - Severe illness (for more information refer to NICE guidelines on sick babies of 47)
  - Poor urine flow
  - Abnormal or dilated mass
  - Renal scarring
  - Fails to respond to treatment with suitable antibiotics within 48 hours
  - Infection with non-fecal organisms

- Recurrent UTI
  - Two or more episode of UTI with acute pyelonephritis upper urinary tract infection
  - One episode of UTI with acute pyelonephritis upper urinary tract infection plus one or more episodes of UTI with symptoms upper urinary tract infection
  - Three or more episodes of UTI with control over urinary tract infection

Summary of recommendations

- Benefits of diagnosing most UTIs are limited
- Test urine based on level of concern about UTI (probability x severity)
- For most children, ultrasonography or no imaging is needed
- Prophylactic antibiotics an option for < 2 year olds (whether or not there is reflux)
- Consider VCUG if sono abnl, or infections are recurrent or severe and age < 6-12 months
After a first uncomplicated febrile UTI in a 15 month old girl with no other indications, would you recommend a VCUG

A. Always
B. Almost always
C. Usually
D. Sometimes
E. Rarely
F. Never

References (in order cited)
Supplementary slides

Cystoscopic injection of dextranomer/hyaluronic acid (Deflux®)*

- Swedish Reflux Trial: Grades III and IV reflux, ages 1 to <2 years
- Improvement in VUR in 71% vs ~43% with abx or waiting (NNT ~ 3-4), P <0.001
- Decreased infections (21% vs 37%; P=0.06; NNT ~6 x 2 yr)
- Not blinded, but not industry sponsored
VCUG is Physically and Emotionally Traumatic

- Distress -- “Children’s memory for features of a voiding cystourethrogram were examined because this invasive procedure is similar in many respects to incidents of sexual abuse.”


Relevant Quotes

- “Reflux does not seem to be a predisposing factor for the development of UTI or a contributory factor inducing renal parenchymal scars in patients with acute pyelonephritis.”

Relevant Quotes

- “Operation and long-term antibiotic prophylaxis are equally ineffective...We have at present no scientific basis on which to tell our patients and their parents that their reflux needs to be [treated]...It is psychologically difficult to accept results that suggest that time-honored methods that are generally recommended and applied are of no or doubtful value.”
Relevant Quotes

- “[VCUG] is often emotionally traumatic… carries a small risk of introducing infection… and involves ionizing radiation. In the absence of controlled studies to demonstrate that either prophylaxis or antireflux procedures are superior to early diagnosis of intercurrent infection and short courses of appropriate treatment, it is difficult to persuade doctors and parents that [VCUGs] are really necessary…”
  -- Verrier Jones, K Arch Dis Child 1995;72:255

Relevant Quotes

- “It’s time to question the routine use of an invasive test for what some experts call an ‘innocent bystander.’”
  -- Ortigas AP, Cunningham AS. Three facts to know before you order a VCUG. Contemp Peds 1997; Sept:69-79.

Relevant Quotes

- “An appreciation of the epidemiology of ESRD… should lead to reconsideration of the imaging evaluation of the urinary tract recommended for a pediatric patient following a UTI.”
Relevant Quotes

This study suggests that the currently advocated treatment of vesicoureteral reflux in children, which is invasive and costly, may be of no benefit in the prevention of ESRD.


References