Issues in the management of UTI in children

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The most frequently occurring SBI during childhood
UTI hospitalizations in US $180 million annually
As many as 5% of all children younger than 2 years who present to the emergency department with fever have a UTI.
General practice not in compliance with guidelines

The Burden of Proof

Scientific uncertainty remains regarding many aspects of preventing adverse outcomes of UTIs. Unanswered questions include the effectiveness of long-term antibiotic use in preventing UTI recurrence or renal scarring, the ability to identify which at-risk patients would most benefit from this intervention, and whether it is safe to wait for a second UTI before intervening with antibacterial prophylaxis (Beetz 2006 [S]).

Asymptomatic Bacteruria

Transient colonization of the bladder- usually resolves without sequelae
>100,000 cfu of same organism on two consecutive specimens in an infant or child without symptoms of a UTI
Hoberman and Wald (1998) - treating asymptomatic bacteriuria increases the risk for a symptomatic UTI.

Febre UTI

Fever(>100F) has defined diffuse pyogenic infection of the pelvis and parenchyma of the kidney
Abrupt onset
Older child: chills, costovertebral angle or flank pain +/- cystitis symptoms
Infants and young children -poor appetite, failure to thrive, lethargy, irritability, vomiting, or diarrhea
Cystitis -inflammatory condition of the bladder
dysuria, frequency, urgency, malodorous urine, enuresis, hematuria, and suprapubic pain

Pyelonephritis vs. Cystitis

ESR/CRP, WBC not reliable especially in young children
Imaging studies – DMSA renal scintigraphy is the imaging study of choice to confirm or exclude the diagnosis of pyelonephritis as well as to detect renal scarring
Procalcitonin-116 amino acid propeptide devoid of hormonal activity- elevated in septic shock but normal in noninfectious inflammatory conditions of viral origin and low in healthy individuals
PCT –sensitivity 83% and specificity 93%
CRP-sensitivity 94% and specificity 32%

Pecile,P. Pediatrics 2004: 114:e249-254
Diagnosis

- Presumed - clinical picture and abnormal labs
  - ANY positive result (Nitrite, LE or WBC /hpf)
- Definite – clinical picture with positive culture growth of single organism
  - SPA >1000 cfu
  - TU cath >10,000 cfu
  - CCM >100,000 cfu

Prevalence

- 2-3% of all children every year.
- Prevalence of UTIs in the first 3 months of life is estimated to be as high as 7.5%.
- <1 yr boys - 3%, girls 7%
- >1yr boys- 2%, girls 8%
- Uncircumcised males -10 fold increase of developing a UTI than circumcised males

Pathogenesis

- Bladder function - complex balance of urine storage and emptying.
- High Risk factors
- Anatomic abnormalities
  - vesicoureteral reflux (VUR): flow of urine in a retrograde fashion-not increase risk for infection but increase risk for complications of infected urine
  - neurogenic bladder-improper storage, incomplete bladder emptying, and potential high-pressure systems.
  - Uncircumcised males - prepuce harbors organisms
- Physiologic factors
  - dysfunction of voiding - Infrequent voiding and incomplete bladder emptying
  - Constipation – chronic retention of stool in rectum leads to higher levels of bacteria colonizing the perineum.

Etiologies

- Bacterial infections are the most common cause of UTIs.
  - E coli is the most frequent pathogen, causing 75-90% of UTIs.
  - Klebsiella species
  - Proteus species - males?
  - Enterococcus species - <30 days
  - Staphylococcus aureus - <30 days
  - Streptococcus group B - uncommon except for neonates
  - Enterobacc sp - <2% of UTI
  - Pseudomonas aeruginosa - <2% of UTI
  - Enterocci sp - <30 days
- Fungi (Candida species), especially after instrumentation of the urinary tract
- Adenovirus (rare)

Vescicoureteral Reflux

- Retrograde urine flow from bladder to ureters - most common functional abnormality of UT in children
  - Short mucosal tunnel length
  - Grades 1-5
  - 20-50% penetrance of VUR in asymptomatic family members.
- Prevalence
  - VUR found in 30-40% of children with UTI compared to 1% prevalence in general population

Figure 1 Diagram of the bladder sub mucosal tunnel

History

- 1960s – pyelonephritic scars noted to be etiology of 50% of hypertension and 30% of ESRD in children
- 1990s – scars account for 5% hypertension in USA
- 1992 International Reflux Study (RCT medical vs. surgical of G3/4) – no difference in scarring
- 1999 AAP Guidelines published
- 2007 National institute for Health and Clinical Excellence Guidelines
- 2008 RIVUR study

What does the AAP guideline miss?

- <2 months
- >2 years
- Recurrent infections

AAP Policy
PEDIATRICS Vol. 103 No. 4 April 1999
Urinary Tract Infections in Febrile Infants and Young Children

- Summary of 11 Recommendations
- Who Should Be Evaluated for UTI?
  - All febrile children ages of 2 months to 24 months with no obvious cause of infection
  - with the exception of circumcised males older than 12 months.
- Minimal Test Characteristics of Diagnosis of UTI
  - Bag specimen not adequate to diagnosis UTI, Culture is necessary to diagnose UTI by a reliable method – bladder cath or SPA
- Treatment of UTI
  - Parenteral treatment if toxic or dehydrated and considering hospitalization.
  - Treat 7-14 days total
- Evaluation of the Urinary Tract
  - Available data support the imaging evaluation of the urinary tracts of all 2- to 24-month-olds with their first documented UTI.
  - Imaging should include VCUG and renal ultrasonography.

<2 months - Imaging in male neonates with UTI

- <2 months especially males presenting with UTI – higher incidence of structural abnormalities.
- Most common VUR, double collecting systems, PUVC, focal scars, renal atrophy.
- 12/45 with abnormal US- 8/12 had normal prenatal US
- E-Coli 62%, 20% bacteremic
- 1991 Royal College of Physicians- US, VCUG, DMSA in all <1yr and US, DMSA in 1-7 yrs
  - They concluded US/VCUG with initial UTI- DMSA if US abnl or VUR III or greater.

>2 years

- Children with UTI in whom renal scars are found – those are visible on the first set of imaging studies and original scars remain unchanged irrespective of the child’s future clinical course.
- Children treated for UTI who have evidence of VUR are significantly more likely to develop scars than are children who do not have VUR.
- More severe reflux is associated with a greater risk of scarring.
>2 years

- Infants and young children are more prone to scarring than are children > 5 years and adults.
- Nearly all new scars in children with VUR occur before the age of 6 years and almost always in association with new UTIs.
- A long-term follow-up study of children who had grade III or IV reflux managed either medically or surgically found incidence of new scar formation over a 5-year period:
  - 20% in children < 2 years
  - 10% in children 2 and 4 years
  - 5% in children > 4 years

Recurrent UTI

- >2 infections in a 6 month period
- Seem to be independent of whether a patient has a preexisting anatomic abnormality:
  - More likely biologic predisposition
  - Underlying causes bacteriuria
    - Dysfunctional voiding syndrome (incomplete bladder emptying, urinary stasis and high bladder pressures)
    - Constipation
    - Neurogenic bladder
    - Surgically correctable- foreign bodies, calculi, urachal cysts, urethral diverticulum, ureteral duplication or ectopic ureters, fistulas (vesicointestinal, urorectal, vesicovaginal)

That was then…Bottom Up approach

- Reflux nephropathy – parenchymal kidney disease associated with VUR
- Considered to predispose to hypertension, ESRD, complications during pregnancy.
- Perception that damage is linked with VUR in context of infection. (triad- UTI/VUR/RN).
- Focus on detection of VUR and prevention of infection in the context of VUR.

Recommendation 10

After a 7 to 14-day course of antimicrobial therapy and sterilization of the urine, infants and young children 2 months to 2 years of age with UTI should receive antimicrobials in therapeutic or prophylactic doses until the imaging studies are completed (strength of evidence: good).

Recommendation 11

Infants and young children 2 months to 2 years of age with UTI who do not demonstrate the expected clinical response within 2 days of initiating appropriate empirical therapy and who continue to have a positive urine culture post-therapy should undergo either a voiding cystourethrogram (VCUG) or retrograde pyelography (RPG) at the earliest convenient time. Ferric and iron tablets, when taken concurrently with an expected increase in phlebotomized blood volume, should be discontinued 1 to 2 weeks prior to a VCUG or RPG performed at a time when the patient is consuming a normal diet.

For medical management of First Urinary Tract Infection in children 12 years of age or less

- Changes to the guidelines made in November, 2006
- Based on literature review conducted in 2006
- see Development Process section for updates
- Effective Publication Date: April 10, 2005
- Effective Publication Date: March, 2009
Why Image?

- Localize infection
- Identify VUR
- Detect renal scars
- Identify structural anomalies
- Presume findings will sufficiently influence management to justify the burden of testing

Questions

What is the meaning of the association b/w VUR and UTI?

Does VUR increase likelihood of renal scars?

Does treatment of VUR decrease likelihood of renal scars?

Is ESRD attributed reflux nephropathy due to UTI in VUR or is it congenital or prenatal?

Does Treatment of VUR in Childhood Prevent ESRD Attributable to Reflux Nephropathy?

Craig J. Pediatrics 105:6 June 2000

- 30% newborns with VUR have renal parenchymal damage even before a UTI (prenatal sono).

- 12-38% sibs of children with VUR who also have VUR (but no UTI) have renal parenchymal damage.

- Primary pathogenic event in individuals who develop ESRD from reflux nephropathy may be congenital and developmental rather than acquired.
Primary VUR as a predictor of Renal Damage in Children Hospitalized with UTI –Systematic Review & Meta

Gordon, I JASN 14:739-744,2003
- Systematic review and meta-analysis
- Lit search 1966-2002 – 12 studies
- Looking at inpatients/most with imaging within 6 wks of UTI bias toward more ill
- 537 patients- VUR in 34%, abnl DMSA 59%
- Some DMSA noted defects associated with acute pyelonephritis resolve w/in 6 months
- Primary VUR poor predictor of renal damage (as identified on DMSA)
- Often present in absence of VUR
- Makes VCUG as a screen for getting DMSA problematic
- US/VCUG still important for flow issues
- We don't really know the prognostic data on DMSA +
- Scars in the absence of VUR
- EColi ascending pyelonephritis vs. hematogenous source
- Scars from old damage (pyelo) and not acute UTI
- Congenital renal parenchymal disease- renal dysplasia/hypoplasia-VUR regresses but other dysfunction persists

Recurrent Urinary Tract Infections in Children Risk Factors and Association With Prophylactic Antimicrobials
Conway,P: JAMA, July 11, 2007—Vol 298, No. 2
- Primary care pediatric practices <6 to 6 years diagnosed with first UTI
- White , 3 to 5 years, and grade 4 to 5 VUR were associated with increased risk of recurrent UTI.
- Sex and grade VUR(1-3) were not associated with increased risk of recurrence.
- Antimicrobial prophylaxis was not associated with lower risk of recurrent UTI
- Prophylaxis was associated with increased risk of resistant infections

Is antibiotic prophylaxis in VUR effective in preventing pyelonephritis and renal scars: RCT
- <30months with VUR (grades 2-4)-100 pts : after acute pyelonephritis (clinical dx)—randomized to prophylaxis(temp/smx) vs. not x 2yrs
  - VCUG 2 mo after acute pyelonephritis
  - RUS, DMSA 6 months after
  - Outcome recurrence of pyelonephritis- 4 yr f/u
  - No differences in risk of having 1 episode recurrence b/w groups, renal scars at end of f/u same in both arms.
- Concluded: continuous prophylaxis ineffective in reducing pyelonephritis’ recurrence and incidence of renal damage

Clinical Significance of Primary VUR and Urinary Antibiotic Prophylaxis after Acute Pyelo: Multicenter, RCT
- 3mo-18yrs - diagnosis acute pyelonephritis on DMSA scan- 218 patients
- VUR (grades 1-3) diagnosis established on VCUG
- Randomized to antibiotic prophylaxis or no prophylaxis
- 1yr f/u- DMSA at 6 mo or with recurrence UTI, UA/UCx every 3months, US/VCUG at 1 yr.
  - no benefit of antibiotic prophylaxis for preventing recurrent UTI, pyelonephritis, or scarring in children with or without reflux
  - Overall recurrence UTI was 20% no differences b/w +/- VUR or +/- antibiotic prophylaxis
  - Most recurrences cystitis
  - 13 pyelonephritis
  - 13 developed renal scars not present at onset ( 7 with VUR III and 6 without VUR)
- Increased incidence of pyelonephritis with resistant strands in prophylaxis group
- Longer length of treatment in this study

The majority of the 611 children -female (543 [88.9%]),white (343 [56.1%]), and aged 2 to 6 years (375 [61.4%]). Most did not have a VCU performed (400 [65.5%]) and had not received antimicrobial prophylaxis (483 [79.1%]).
- Children younger than 2 years were more likely to have a VCU performed (137 [58%]) compared with children older than 2 years (75 [20%]).
- Of the 68 male children, there was no documented circumcision status for 32 (47%). Twenty-six (38%) were uncircumcised and 10 (15%) were circumcised
Top Down – focus on the kidney

- Focus on detecting renal inflammatory involvement during a clinical episode of pyelonephritis using DMSA as cornerstone.
- Alternative theory- association of VRU/reflux nephropathy and ESRD removing the UTI (potentially preventable) component.
- 30% newborns with VUR have renal damage detectable before UTI has occurred= congenital renal dysplasia/hypoplasia.
- Family studies of VUR- genetic basis of many malformation sequences—renal damage present in 12-38% of siblings (with no history of UTI).

Revisit conclusions

- Strategies to correct VUR or to prevent UTI to decrease Reflux nephropathy-no impact on ESRD
  - may be more important to identify and treat acute UTI early and accurately
  - Use of a modified imaging algorithm may be more sensitive to detect those at risk for renal damage with less costly and invasive intervention
  - VUR-Reflex nephropathy-ESRD pathway is real but may occur independently of UTI in most cases.
- Risks of antibiotic overuse with little evident benefit
- Excepting special populations

More to come...

- Updated AAP policy statement
- No studies of the efficacy of prophylaxis in High Grade Reflux.
- Role of Deflux.
- Results of the RIVUR study

Thank you

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Colleagues