**MT**

- 2 year old girl with fever, irritability, and grabbing perineum with voiding
- Poor oral intake, vomited x2
- Urine shows 3+ leukocytes, 2+ nitrates, WBCs and culture grows >50,000 E. coli
- Antibiotics?
- Ultrasound?
- VCUG?

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**Pediatric UTIs, Reflux, and Guidelines:**

*Seeing the Forest and the Trees*

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**UTI: Significance**

- Incidence estimated at 8% in girls and 2% in boys through childhood
- By age 1, 2.7% of boys and 0.7% of girls have had bacteriuria
- 40% require hospitalization
- 40% transient renal damage
- 5% permanent renal damage, sometimes after single infection
- Up to 30% recurrent
- 13/100,000 infants and 53/100,000 children hospitalized annually for UTI
- UTIs accounted for 2.4 to 2.8% of all physician visits for children

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**“Standard” Treatment of VUR**

- Continuous antibiotic prophylaxis (CAP) awaiting spontaneous resolution
- Periodic re-evaluation for VUR status and renal scarring
- Surgical correction for breakthrough UTI, persisting VUR after observation, anatomic abnormality restricting resolution
  - eg. diverticulum

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**Pediatric UTIs and Reflux: A Sea Change**

- Historical momentum directed us to look for reflux in order to prevent the damage that was so common in years past by using prophylaxis and surgery
- Recent studies have questioned the value of prophylaxis in preventing UTI, and thereby the value of diagnosing reflux
- Reflux was seen as relatively benign

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**Historical Perspective:**

*Prognosis of Childhood Urinary-Tract Infection — The Current Status of Patients Hospitalized between 1940 and 1950*

Robert E. Steele, Jr., Guy W. Leadbeater, Jr., and John D. Crawford
N Engl J Med
1963; 269:883-889

- 11 to 27 year follow-up of 72 children hospitalized for UTI
  - 8% progressive renal failure
  - 22% persistent untreated or recurrent UTI
  - 18% dead
  - Of males who died, 73% within 1 month of initial UTI diagnosis
Challenging the Orthodoxy in Vescicoureteral Reflux: A Perfect Storm

"The greater the ignorance, the greater the disease."
—William Osler

"One of the first duties of the physician is to educate the masses not to take medicines."
—William Osler

Our current management scheme for vesicoureteral reflux (VUR) is being challenged by a "perfect storm" of new data, including the rapid and widespread implementation of antimicrobial prophylaxis in infants, toddlers, and older children. Although the American Academy of Pediatrics (AAP) has published a detailed action statement (Action Statement 6) on the diagnosis and management of VUR, our society of urologists is uncertain how to manage this condition.

AAP UTI Guidelines

- What do they say?
  - Why is there confusion, concern and controversy?
  - What can we do?

AAP UTI Guidelines - 2011

Action Statement 6

- VCUG should not be performed routinely after the first febrile UTI
- VCUG is indicated if the RBUS shows hydrenephrosis, scarring or other findings suggestive of high grade VUR or obstruction
- Further evaluation should be conducted if there is recurrence of febrile UTI

If Continuous Antibiotic Prophylaxis (CAP) is not effective in preventing UTI with Reflux, there is no rationale to diagnose VUR

AAP UTI Guidelines - 2011

Action Statement 6

Several studies have suggested that prophylaxis does not confer the desired benefit of preventing recurrent febrile UTI. If prophylaxis is ineffective in VUR management, then the rationale for performing VCUG routinely after an initial febrile UTI must be questioned.
Attempts to Validate

- 3 RCTs from 1966-2001
  - Savage 1975, Stansfeld 1975, Smellie 1978
- Verdict: Too many confounders
  - Mostly females age 6 months to 14 years
  - Almost all children with recurrent UTI and normal upper tracts
  - Treatment range from 10 weeks to 12 months
  - 2 without blinding
  - None used intention-to-treat analysis
- Diagnosis criteria inconsistent and poor
- "The small number of poor quality studies gives no reliable evidence of the effectiveness of antibiotics in preventing recurrent UTI."

Antibiotic Prophylaxis (CAP) for Reflux

<table>
<thead>
<tr>
<th>Study</th>
<th>UTI (%)</th>
<th>CAP</th>
<th>No CAP</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garin et al. (n=113)</td>
<td>23.6</td>
<td>22.4</td>
<td></td>
<td>Wide age range, low grade VUR</td>
</tr>
<tr>
<td>Roussey-Kessler et al. (n=223)</td>
<td>NO BENEFIT</td>
<td>FOR CAP</td>
<td></td>
<td>Low grade VUR, uncertain compliance; UTI definition loose; benefit for boys with Grade III VUR</td>
</tr>
<tr>
<td>Perrenesi et al. (n=100)</td>
<td></td>
<td></td>
<td></td>
<td>Included crossover</td>
</tr>
<tr>
<td>Montine et al. (n=338 – 128 with VUR)</td>
<td>12</td>
<td>20</td>
<td></td>
<td>First febrile UTI; difference not statistically significant</td>
</tr>
<tr>
<td>Craig et al. (n=576 – 221 with VUR)</td>
<td>13</td>
<td>18</td>
<td></td>
<td>43% with VUR, benefit seen in VUR sub-group; statistically significant effect of CAP</td>
</tr>
</tbody>
</table>

Limitations: small numbers in many, limited power, definitions of UTI variable and included "bag" specimens, lower grades of VUR in many, no assessment of voiding dysfunction, short follow-up (1 to 2 years)

AAP UTI Guidelines

- What do they say?
- Why is there confusion, concern and controversy?
- What can we do?

Why should we be concerned about the recommendation NOT to perform a VCUG after the first febrile UTI?

- Data and interpretation are flawed
- Inadequate safety net
- Guidelines are not "real-world"
Data and interpretation are flawed

Evidence Based Medicine

• How good is the evidence?
  ✓ wide age ranges,
  ✓ few patients with higher than grade II VUR,
  ✓ variable culture methods,
  ✓ low incidence of initial renal abnormalities,
  ✓ no assessment of medication compliance,
  ✓ no assessment of voiding dysfunction

• “...the studies were insufficiently powered for an analysis according to the grade of reflux.” Monbi et al., NEJM, 2011

“Beware the False Prophet of the Small Study”

• Most of the prior studies included small numbers with highly variable definitions and outcome criteria
  • Many variables contribute to the occurrence of infection – the most common outcome parameter
    – Local antibiotic resistance, circumcision status, genetic patterns of reflux, history of infections, timing of studies
    – Very difficult to control for all of these

Combining Studies

Combining data from multiple flawed studies introduces multiple statistical risks

• Amalgamation paradox (Simpson’s Paradox)
  ✓ Result of combining studies of differing sizes
  ✓ Often due to a “lurking” variable that is not accounted for
    ? Bladder/bowel dysfunction

Antibiotic Prophylaxis for the Prevention of Bacteriuric urinary tract infection in Children With Low Grade Vesicoureteral Reflex: Results From a Prospective Randomized Study

• Confounders
  ✓ “we observed a relatively high rate of UTI related to an organism sensitive to cotrimoxazole in children treated with such antibiotics”
  ✓ “voiding pattern was not explored”
  ✓ “most boys were uncircumcised”
  ✓ Sterile bag collection for non-toilet trained and mid-stream for toilet trained monthly

Swedish Reflux Trial: J. Urol. 184:286, 2010
What is the risk of missing reflux?

Overall scarring incidence is "low" - but is it low enough?

- Scarring can be severe - Coulthard (Ped Nephrol 2009)
- Pyelonephritis and scarring can occur without reflux, but reflux increases the risk by a factor of at least 2.6
- Grade of reflux correlates with scarring risk
- Number of infections correlates with scarring risk
- Delays in therapy can be associated with more renal injury

Acute Pyelonephritis and Renal Injury is Increased with VUR

- In rigorous studies with initial DMSA showing acute pyelonephritis and comparing incidence of permanent scarring (at 6 months post UTI)
- Presence of reflux increases risk of permanent scarring after episode of pyelonephritis by
  - 2.8 times for patients
  - 3.7 times for renal units

Early treatment and evaluation reduces scarring

- More aggressive referral, treatment and evaluation of children with febrile UTIs was associated with half as many scars in refluxing children
Guidelines are not “real world”

This is the real world...

- 70% adherence to recommended method of urine collection
- 61% adherence to recommended imaging work-up

Is this a Real UTI?

- 2 year old uncircumcised boy
- Diuresis
- Fever to 102
- Fussy but taking PO well

In the “Real” world...

- Do patients and families always remember how many infections they have had?
- Do we always have the necessary documentation of a UTI?
- Do families always see the same pediatrician or care giver?
- Do transient families have access to an informed provider and to their own records?

Why should we be concerned about the recommendation NOT to perform a VCUG after the first febrile UTI?

- Data and interpretation are flawed
- Inadequate safety net
- Guidelines are not “real-world”

Why do we differ?
Perceptual problems

- Reflux is being "decriminalized" and seen as a **homogeneously** "benign" condition
- This is the same narrow view as that in which all reflux was seen as "dangerous"
- UTI is a warning sign for risk; ignoring it once may send the wrong message to family and practitioner
- A diagnosis of VUR improves the ability of the family and pediatrician to respond appropriately

UTI’s, VUR and CAP

- How do we reconcile these highly variable study results?
- Does this apply to all reflux patients, or only some?
- Can we figure out which ones?

Management and Screening of Primary Vescoureteral Reflux in Children: AUA Guideline

Bladder and Bowel Dysfunction (BBD): Etiology

- **Holder**
  - Too busy to go
  - Hurts to go
- **Unstable bladder** (Urge syndrome)
  - Immature bladder; always creating an urge to void
  - Resisted with toilet training
- **"Lazy" bladder**
  - Inadequate emptying; over-flow wetting, infections

Dysfunctional Voiding – Bladder and Bowel Dysfunction (BBD)

UTI incidence with CAP: Impact of Bladder and Bowel Dysfunction

- 43% incidence if BBD present vs. 12% if no BBD
What might contribute to infection and reflux persistence?

- Healthy 5 year old girl with history of multiple febrile UTIs
- Evaluation deferred by parents
- History of holding behavior, delayed voiding, wetting and constipation
- Physical examination normal
- Outside RUS interpreted as normal
- Begun on voiding retraining

BBD, UTI and Reflux

- Follow-up cystogram immediately pre-op 7 months later
- No reflux, good emptying – no surgery
- Fewer infections; none febrile; no VUR on re-test

RIVUR

Randomized Intervention for Children with Vesicoureteral Reflux

- NIH/NIDDK sponsored clinical trial on the efficacy of prophylactic antibiotics in children with VUR
- 1 Data coordinating center, 5 Clinical treatment centers, 40 participating sites
- 2 year study with incidence and character of UTI as primary endpoint and renal scarring, treatment failure, and antimicrobial resistance as secondary endpoints

RIVUR: Conclusions

- Continuous antibiotic prophylaxis reduces the risk of recurrent febrile UTI in children with VUR
- Initial febrile UTI presentation and presence of BBD predicted more effectiveness for CAP
- No effect on renal scarring was demonstrated
- Those children with breakthrough infections were more likely to have a resistant organism
RIVUR: Limitations

- Low baseline scarring incidence – low risk population
- TMX-SUL may have more resistance in the US – nitrofurantoin has been seen to be a more robust prophylactic agent

RIVUR: What does it tell us?

- Prophylaxis is a useful intervention to prevent recurrent UTI in children with VUR
- There are minimal risks to CAP
- BBD is a risk factor for febrile UTI
- CAP may prevent scarring from febrile UTI and VUR, but this will need to be more clearly proven in a population at greater risk for scarring
- Pediatricians and urologists can collaborate on large clinical studies

Clinical Management of UTIs: 2017

- Much uncertainty
- The AAP Guidelines recommend a significant change in practice
- Patients with UTI, pyelonephritis and reflux are here today
- We are treating individual children, not radiographic images or statistics
- Children tend to ignore statistics

AAP UTI Guidelines

- What do they say?
- Why is there confusion, concern and controversy?
- What can we do?

Can antibiotic prophylaxis prevent UTI and renal injury?

- Yes, in some children, but...
- It may not be needed in all children with reflux
- Benefits those with higher risk of UTI: prior UTI, scarring, BBD

Should we look for reflux, and if found, treat it?

- If some children can benefit in terms of preventing recurrent febrile UTI and renal injury,
- Reflux should be sought and treated in those at most risk.
- Who are those at risk?
Risk Assessment in the Child with a First Febrile UTI

- Is this a real UTI?
- Was the child toxic?
- Does the child void normally? Constipated?
- Is the “normal” ultrasound reading reliable?
- Are the parents going to come back with another episode?
- Are you and the parents comfortable to monitor without further imaging?

Grade 3 Reflux

- 2 year old girl with fever, irritability, and grabbing perineum with voiding
- Poor oral intake, vomited x2
- Urine shows 3+ leukocytes, 2+ nitrates, WBCs and culture grows >50,000 E. coli
- Antibiotics?
- Ultrasound?
- VCUG?

Reflux and Risk of UTI
Summary

• The clinical diagnosis of UTI should be rigorous
• UTI evaluation should be tailored to the child and their risk of recurrence and renal injury
• Collaborative decision-making with parents, pediatricians and specialists
• There is evidence that CAP can be effective in the child at higher risk for UTI
• We should not forget what has been learned about reflux and its risks

Seeing the Trees and the Forest

• The most appropriate care for children with UTI is to recognize the importance of seeing the individual and their potential risk, and recognizing differences in parental risk perception and aversion...
• in the context of knowing the broad patterns of clinical outcomes, the impact of antibiotic use on the community, and to be cost-conscious.

Those who do not remember the past are condemned to repeat it.

George Santayana