Controversies and Challenges in the Management of Urinary Tract Infections

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Disclosures

I have no relevant financial relationships to disclose.
Goals

• Complex scenarios often arise in management of UTI’s
• I would like to address 3 challenging issues
  – The child with **Recurrent UTI**
  – The child with **chronic bacterial colonization**
  – The **guidelines for evaluation** of pediatric UTIs

(The type of cases you will often encounter but wont easily find the answers in a text book)
Challenging Scenario #1
Persistent UTI

• EH is 7 y.o. girl afebrile RUTIs for years
• Symptoms of infection: only odor, dysuria
• 2014 **Renal US**: normal. **VCUG**: normal
• Abx prophylaxis started with success – stopped 1.5 yrs ago.
• Persistent UTI since Nov 2017 due to Ecoli.
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Renal US
4 considerations in child with RUTI

• Bladder
• Bowel
• Physical Exam
• Urinalyses
  – Clarity, Spec Gravity, protein
  – Microhematuria
  – LE and WBC’s
  – Culture results
Bladder

• Her Bladder Symptoms
  – Daily Urinary urgency
  – Small frequent amounts of urge incontinence
  – No nocturnal enuresis
  – Occasional dysuria

• Bladder Spasms
  – Most common cause of RUTIs
  – Most common cause of non-UTI bladder symptoms
  – The frequent small leakage between labia causes inflammation that causes dysuria
  – Labial inflammation notoriously contaminated UA’s
• “No issues with constipation”
• Upon further questioning
  – Hard BM
  – Abd pains. Rectal pain with BM
  – “Man size poops”
  – Occ. Blood on toilet tissue
  – Occ. clogging of toilet

• Rarely do I get an accurate bowel history on first questioning
Physical Exam

• Overweight
  – Genitalia: Labia were chubby and urethra and vagina recessed
  – Red and inflamed
  – Moisture between labia upon separation

• Vaginal Voiding
  – Common cause of contaminated collection.
  – Impossible to collect a clean UA
  – “We did a urinalysis today. It shows moderate blood, nitrite negative, and a trace of leukocytes.” It is sent for culture. Note that her bottom was quite red today and we may very well get a contaminated culture report” C. Durkee
## Urinalysis

- **Clarity, spec gravity, protein**

### Table: Urinalysis Results

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### Note:
- Consistently high urinary concentration
- Relationship of Clarity, Concentration, and Protein
Microhematuria

- True that UTI can cause microhematuria
- However more true that chronic constipation and vaginal inflammation cause microhematuria

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## Leukocyste Esterase, WBC's, and Culture Results

### Note:
- Drug resistant organisms worsened as time went by with recurrent courses of abx
- Bacteria and WBCs can colonize the introitus and vagina
- Squamous Epi’s (-) in all

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Considerations in child with RUTI

• Bladder Spasms
  – May be the cause of the symptoms
  – May be a cause of RUTIs

• Bowel
  – Do not trust initial history…dig deeper
  – Constipation is gas on the fire to an overactive bladder

• Physical Exam
  – Labial inflammation and chronic wetness

• Urinalyses
  – Can be helpful and misleading at same time
Challenging Scenario #2
Chronic bacterial bladder colonization

- JG is 12 yo boy with neuro bladder due to Spina bifida
- On Clean Intermittent Cath (CIC) 5x/day
- Frequently treated for UTI based on parent perception of fatigue and low grade temp.
  - Problem is, the urine is always colonized 7 days a week and will have a (+) Urine Culture

- So when do you treat with antibiotics?
## Urinalyses (Over past year)

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<th>Date</th>
<th>Sp Gravity</th>
<th>Urine Bacteria</th>
<th>Urine Blood</th>
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<th>Urine Color</th>
<th>Urine Leuks</th>
<th>Urine Nitrites</th>
<th>Urine pH</th>
<th>Urine Protein_</th>
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Neurogenic bladder due to:

- Spina bifida
- Tethered spinal cord
- Spinal cord injury
- Transverse myelitis
- Chiari malformation (hydrocephalus)
- Brain tumors
- Others
Clean Intermittent Catheterization (CIC)

- Scheduled evacuation
  - Lapides, 1972 first reported on effectiveness of clean intermittent catheterization for scheduled bladder emptying
  - Life changing QOL tool in the care of children with neuro bladder

Common Problems

• Chronic Bacteriuria
  – Most patients that catheterize are chronically colonized with bacteria
    • Generally benign condition
    • Foul smelling or cloudy urine is common complaint
  – Antibiotics only if symptomatic
    • Fever, new onset urgency or incontinence
  – Antibiotics if Proteus or Pseudomonas
Urinalysis does not determine UTI, symptoms do!

- Urine WBC unreliable
  - Pyuria does not correlate with symptoms in pts on CIC
  - WBC’s in urine vary from early to late drainage samples
  - Colony counts unreliable
    - >100K does not correlate with necessity to treat

Chronic Bacterial Colonization

....Starting clean, intermittent catheterization will frequently result in chronic colonization of the bladder by bacteria. These bacteria are generally of low clinical consequence to urinary tract health if they are evacuated on a regular basis of at least four or more times per day.... **Overuse of antibiotics will contribute to formation of antibiotic-resistant organisms.** The urine culture should be checked periodically for the presence of certain urease-positive organisms, such as *Pseudomonas* and *Proteus*. These are not suitable organisms to colonize the bladder and should be eradicated to minimize formation of urinary tract stones or biofilms[13]. **In general, other bacteria, such as E. coli and Klebsiella sp., can safely colonize the bladder[14,15]...**

The issue....

• There seems to be concern for increasing CAUTI’s
• Some would have you believe this can be eliminated simply by better care of catheters
  – Washing the peri-urethral skin around the cath
  – Keeping the cath drainage bag below the bladder
  – Securing the cath to the leg to minimize slipping
  – Maintaining a closed system
• However the answer is not likely this simple
• Many factors have escalated the concern for CAUTI
  – Public anxiety of hospital acquired infection
  – Increasing incidence of MDR bacteria
  – Increasing use of abx
  – Health care costs attributed to hospital acquired infection
  – Insurance penalties for hospital readmissions
  – National rankings by various accrediting bodies. (US news, NSQIP, SPS, …)
Conclusions: No consensus exists for the evaluation and management of bacteriuria in patients with spina bifida and neurogenic bladder at clinics specializing in the care of such patients, even at those with established standards of care. A clear need exists for an established, national set of evidence based guidelines to assist medical decision making in this high risk population and, thus, improve care.

- My best advice is use good clinical judgment in collaboration with pediatric urology
- Don’t look for an answer in a guideline or a textbook for these unique patients
- Treat when Fever >102 or new onset of urinary urgency or incontinence
- Otherwise observe for 1 or 2 or 3 days and see what happens
- Never assume symptoms are due to urine just b/c culture (+)
What are best guidelines for evaluation of Pediatric UTI?
Fundamental Goals for management of VUR have not changed

- Minimize Renal Scarring
- Minimize recurrent UTI’s
  - Avoid unnecessary surgery and anesthesia
  - Avoid unnecessary medication
  - Contribute to cost-effective health care
Traditional Approach

- Evaluation of pediatric febrile UTI
  - Renal US + VCUG
    - After 1st febrile UTI in all boys of any age
    - After 1st febrile UTI in all girls under 5yo, or RUTIs under 12 yo

- Screening VCUG for all neonates with significant hydronephrosis
- Screening sibling of refluxers in some circumstances

- Use of Abx prophylaxis
  - Prophylaxis was recommended in children w/VUR under 5yo
  - Prophylaxis for children with recurrent symptomatic UTI w/o VUR (>3/yr)
The Controversy

- A group of studies challenged the long standing paradigm of management for VUR, VCUG, abx prophylaxis

- This resulted in new AAP guidelines

- New guidelines seem potentially flawed and contradictory to current pediatric urology practice and experience

- Thus there is a element of confusion and lack of standardized approach to management

- What is the Best Practice?

6. Craig et al, NEJM 2009
Current AAP Guideline

• AAP revised guidelines 2011 suggested new approach to evaluation of children aged 2-24 months with UTI
  – Renal US after 1st febrile UTI, if normal then no VCUG
  – VCUG recommended after 2nd febrile UTI

  o “The Big 6” suggested no benefit of abx prophylaxis among patients with VUR in preventing UTI
  o Therefore prophylaxis is not recommended to prevent febrile UTI
  o Logic: if there is no benefit to prophylaxis, then difficult to justify identifying reflux in infants in first place.
    • So no VCUG

6. Craig et al, NEJM 2009
Why the impetus for change from tradition...?

- The distress of VCUG

- The potential radiation of VCUG
  - In past: *Conventional fluoroscopy unit* corresponds to **12 weeks of background radiation**
  - Currently: *Contemporary fluoroscopy unit* corresponds to **7 days of annual background radiation** (at sea level in the USA);
    - equals about **0.1 mSv**;

- Screening for VUR in children with prenatal hydronephrosis and siblings of refluxers may have overdiagnosed large numbers of patients at low risk for UTI and/or scarring

- Since the 90’s we see fewer children with significant scarring at presentation.... thus less fear of the sequelae of VUR and scarring
What History has taught us about Renal Scarring

• One of the most active areas of pediatric urologic research in the 1980’s
• Renal scarring, the result of inflammatory sequelae
  – Renal ischemia
  – Toxic metabolites
  – Oxygen-derived free radicals
• Renal scarring may be prevented or diminished by early abx for pyelonephritis

4. Smellie, Edwards 1985
5. Skoog, Belman, Majd 1985
What History has taught us about Renal Scarring

- Acquired Renal scars are due to **pyelonephritis**
- Sterile reflux not assoc. with renal scarring
- Children w/VUR may also harbor congenital “scars” of renal dysplasia
- Risk of scarring greatest in infancy

1. Jakobsson, Berg, Svensson 1994
2. Rushton, Majd 1992
5. Ransley and Risdon 1978
UTI’s

- Uti’s are ascending infections that arise from peri-urethral colonization of intestinal flora
  - Pathogenic bacteria characterized by adhesive properties such as p-fimbria and other virulence factors
- Children harbor p-fimbriated E.coli fecal isolates frequently
- Hematogenous source of pyelonephritis is rare

1. Stamey 1976
2. Bolgren 1976
3. Ginsburg 1982
4. Plos 1995
UTI diagnosis

- How we diagnose UTI is critical element of management
- UTI is best diagnosed by combination of
  - clinical symptoms
  - >10 WBC/hpf, and
  - Urine culture >100K organisms.
  - Enhanced by (+) leukocyte esterase and nitrate on dipstick.
  - Any of these alone is less sufficient

- (+) Urine culture with neg (-) UA is usually contaminant

- "Well done" cath >> clean catch >> bag sample
Seeing the Trees amid the Forest

• The answer seems to be that all VUR or UTIs are not the same
• **There are individual patient characteristics (or subsets of patients) that affect outcomes**
• Therefore we should not broadly generalize UTI management for all children with one concept
Pediatric Urology Response
(AAP section on Urology)

1) None of the “Big 6” assessed the impact of not knowing if VUR present (parents may behave differently if they KNOW their child has VUR)

2) Studies did not address abx compliance in prophylaxis cohorts

3) Did not acknowledge the role of voiding dysfunction.

4) Data depended heavily on cultures from bagged specimens

5) Relatively more boys in these studies than the typical spectrum of refluxers
   • Boys are going to do well after 1 year of age whether on prophylaxis or not.

6) Uncircumcised status of boys in European studies
   • Bagged specimens are notoriously inaccurate in these boys
   • Uncirc’d boy may have (+) urine cultures regardless of prophylaxis


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Take me to the RIVUR

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• A Randomized, Double-blind, Placebo-controlled Trial of Antimicrobial Prophylaxis in Children with Vesicoureteral Reflux and Urinary Tract Infection

• **Primary Hypothesis**: The proportion of children with a recurrence of UTI will be lower among those in the antimicrobial prophylaxis group than in the placebo group

• **Secondary Hypothesis**: Lower Renal Scarring in children on prophylaxis
RIVUR Study addressed the flaws of prior studies

  - follow up completed June 2013
- 607 patients, 2-72 mos old
- Median age 12 mos
  - **Gender distribution:** 558 (92%) girls
  - **bladder/bowel dysfunction** present in 56% of toilet trained children in study
  - **VUR**
    - grade 2-3 80%
    - grade 4 8%
    - bilateral 48%
  - **Compliance:** 77% parents gave med at least 75% of time
• Urine collected by catheter or SP aspiration, or clean catch. **No bagged samples**
• **Infection diagnosed by strict criteria** of pyuria, culture proven, and fever or symptoms
• Periodic rectal swabs to assess for Ecoli resistance pattern to tmp/smx prophylaxis
• TMP/SMX prophylaxis significantly lower incidence of RUTI
• In this placebo-controlled trial in children with vesicoureteral reflux after a first or second febrile or symptomatic urinary tract infection, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrence
• No difference in renal scarring between groups
• Patients with Bladder and bowel dysfunction had fewer UTIs on prophylaxis in comparison to placebo group
• Rectal swabs showed no significant difference in the rate of resistance of E.Coli to tmp/smx due to prophylaxis
Summary

- New AAP Guidelines should not be extrapolated beyond children older than 24 mos
- What is the morbidity of presentation to the ER with febrile illness
  - Cost
  - Time
  - Expense to the parent
  - School absence
  - Lost work for parents
  - Catheterization
  - IV pokes
  - Lumbar puncture
- We should not forget history that led to understanding the long-term health consequences of VUR
Summary

• There is flexibility that allows us to individual our therapy to each child/ family
  – “This clinical practice guideline is not intended to be a sole source of guidance for the treatment of febrile infants with UTIs. It is not intended to replace clinical judgment or to establish an exclusive protocol for the care of all children with this condition.”
  • pp. 596-597 of AAP guideline. Pediatrics 2011

• Risk stratification of patients with VUR should be based on:
  – Bladder and bowel dysfunction
  – Febrile or recurrent UTIs

• We should not base general algorithms on the outcomes of flawed studies in the Big 6
Guidelines for UTI work up

• **All infants <2 mos old** with 1st febrile UTI: RBUS and VCUG
• **Boys and Girls 2-24 mos w/ 1st fUTI**: All RBUS
  – VCUG if US is abnormal or if Recurrent fUTI
  – VCUG optional if US is normal. Use clinical judgment
• **Boys and Girls > 2 -5 yo**: same
• **Boys and Girls 5-15 yo**: same
  – Be very aware in this age group of bladder and bowel dysfunction
  – Physical exam findings
  – Urinalysis pitfalls
ABX Prophylaxis Guidelines

- Use of Abx prophylaxis
  - Prophylaxis optional in children w/VUR under 5yo
    - Use clinical judgment based on severity of illness or history of fUTI
    - Parent preference
    - Favor prophylaxis if ureteral dilation, severe hydro (esp. females)
    - Favor prophylaxis for anatomic anomalies like ureterocele, cloacal anomaly, bladder exstrophy (usually peds urology will determine)
  - Prophylaxis for children with recurrent symptomatic UTI w/ or w/o VUR (>3/yr)
    - Especially if bladder and bowel dysfunction
The end