




MT



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







Pediatric UTIs, Reflux, and Guidelines: *Seeing the Forest and the Trees*



Craig A. Peters, MD, FACS, FAAP
 Chief, Pediatric Urology
 Children's Health System Texas
 Professor of Urology
 University of Texas Southwestern
 Dallas, Texas

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
- 174/100,000 infants and 51/100,000 children hospitalized annually for UTI
- UTIs accounted for 2.4 to 2.8% of all physician visits for children






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

Robert E. Steele, Jr., Guy W. Leadbetter, 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



“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*

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

Challenging the Orthodoxy in Vesicoureteral Reflux: A Perfect Storm

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

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

Our current management scheme for vesicoureteral reflux (VUR) is being challenged by a "perfect storm" of new ideas, including the rapid and widespread application of endoscopic therapy, emerging antibiotic resistant organisms and evidence that antibiotic prophylaxis (AP), our mainstay of observational management, may not be effective. Families of patients with VUR and their clinicians are left without clear guidelines as to appropriate treatment of this common condition.

As the efficacy of antibiotic prophylaxis is being challenged, the value of making the diagnosis of reflux has been ineffective in VUR runs counter to experience. We must somehow reconcile evidence based medicine and experience based medicine. Although both have validity and value, they make clinical decision making a challenge.

From an evidence standpoint, the studies of Garin⁴ and Roussey-Kesler⁵ et al are level 1, which is far "better" than the vast majority of reports addressing VUR available in the literature, yet they must be interpreted cautiously. We need to critically evaluate the literature related to reflux by asking 5 questions. 1) Is the population representative of those cases we see in terms of age, grade and presentation? What

J Urol 179:1666-7, 2008

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PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Urinary Tract Infection: Clinical Practice Guidelines for the Diagnostic and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months
SUBCOMMITTEE ON URINARY TRACT INFECTIONS AND STEERING COMMITTEE ON QUALITY IMPROVEMENT AND MANAGEMENT
Pediatrics originally published online August 28, 2011; DOI: 10.1177/0009912211418116

RVR

Randomized Intervention for Children with Vesicoureteral Reflux

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

Revised, 2010

EDITORIAL

Antibiotic Prophylaxis for Vesicoureteral Reflux — Answers, Yet Questions
John R. Ingelfinger, M.D., and F. Braver Stapleton, M.D.

Antibiotic prophylaxis, the appropriate flow of therapy did not include placebo groups. Thus, studies were done in the setting of observation that has been indicated since children with urinary tract infections and

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AAP UTI Guidelines

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

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AAP UTI Guidelines - 2011

Action Statement 6

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

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AAP UTI Guidelines - 2011

Action Statement 6

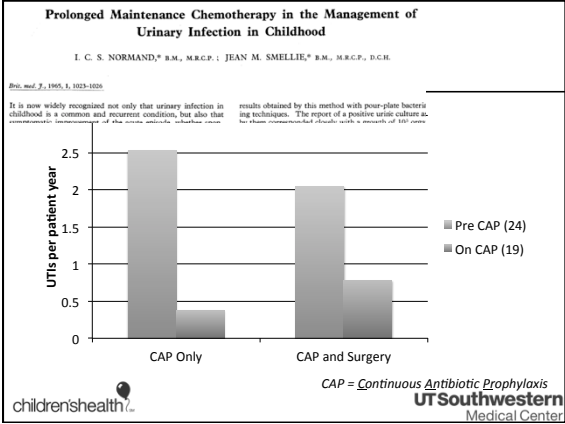
Several studies have suggested that prophylaxis does not confer the desired benefit of preventing recurrent febrile UTI.⁵⁴⁻⁵⁵ If prophylaxis is, in fact, not beneficial and VUR is not required for development of pyelonephritis, then the rationale for performing VCGU routinely after an initial febrile UTI must be questioned.

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



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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."**

Williams GJ, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. *The Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD001534. DOI: 10.1002/14651858.CD001534.

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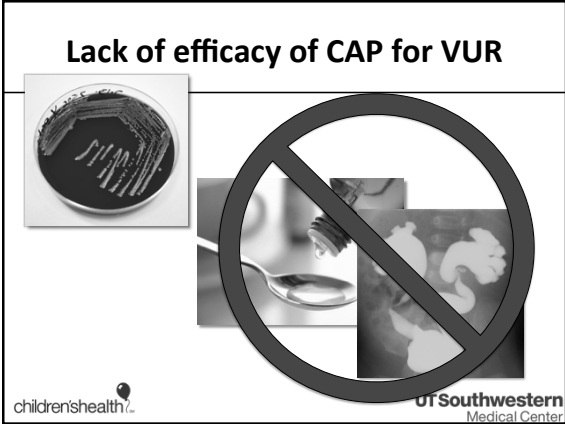
Antibiotic Prophylaxis (CAP) for Reflux

	UTI (%)		
	CAP	No CAP	
Garin et al. (n=113)	23.6	22.4	Wide age range, low grade VUR
Roussey-Kessler et al. (n=223)	28	26	Low grade VUR; uncertain compliance; UTI definition loose; benefit for boys with Grade III VUR
Pennessi et al. (n=100)			Included crossover
Montini et al. (n=338 - 128 with VUR)	12	20	First febrile UTI; difference not statistically significant
Craig et al. (n=576 - 221 with VUR)	13	19	43% with VUR; benefit seen in VUR sub-group; statistically significant effect of CAP

NO BENEFIT FOR CAP

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)

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AAP UTI Guidelines

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

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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"

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Data and interpretation are flawed

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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." *Montini et al., NEJM, 2011*

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"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

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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

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Antibiotic Prophylaxis for the Prevention of Recurrent Urinary Tract Infection in Children With Low Grade Vesicoureteral Reflux: Results From a Prospective Randomized Study
 G. Bouassay-Kudler, V. Gadjeva, N. Idroos, B. Horan, L. Ichay, M. D. Leclair, F. Raymond, A. Griller, I. Hazart, L. de Paracou, R. Salomon, G. Changion, V. Leroy, V. Guignois, D. Siret, J. E. Palcoux, S. Taqie, A. Lemaigro, J. M. Nguyen and C. Guyot

- 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

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Swedish Reflux Trial: J. Urol. 184:286, 2010

Logrank p < 0.0001

1	43	41	38	35	23
2	43	42	40	40	23
3	42	24	20	19	14

Time to first febrile recurrence (months)

— 1: Endoscopic - - - 2: Prophylaxis - · - · 3: Surveillance

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Inadequate safety net

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AS THE FATHER SEES AS THE CHILD SEES AS THE MOTHER SEES

Risk

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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

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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**

Odds Ratio of Scarring with Reflux

AUA Reflux Guidelines - 2010
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Relationship Among Vesicoureteral Reflux, Urinary Tract Infection and Renal Damage in Children

Source: Swerkersson, Ulf Jodal, Rune Sill, Eira Stockland and Sverker Hansson. From the Department of Pediatrics, Pediatric Clinical Physiology and Pediatric Radiology, Pediatric Uro-Nephrology Center, Göteborg University, Göteborg, Sweden

Purpose: We studied the relationship among vesicoureteral reflux, urinary tract infection and permanent renal damage in children.

Materials and Methods: We retrospectively analyzed 900 children younger than 2 years with a first time, nonobstructive...

Number of UTIs and percent with DMSA abnormalities

Number of UTIs	Boys (%)	Girls (%)
0	~25	~25
1	~35	~45
>2	~65	~75

VUR grade and risk of DMSA abnormalities

VUR Grade	Relative Risk
I	~1.5
II	~2.5
III	~3.5
IV-V	~5.5

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Early treatment and evaluation reduces scarring



- Coulthard, et al. *Arch Dis Child* 99:342, 2014
- More aggressive referral, treatment and evaluation of children with febrile UTIs was associated with half as many scars in refluxing children

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Guidelines are not “real world”

This is the real world...



Adherence to AAP Practice Guidelines for Urinary Tract Infections at Our Teaching Institution

Clinical Pediatrics
Volume 47, Number 9
November 2008, 861-864
© 2008 Sage Publications

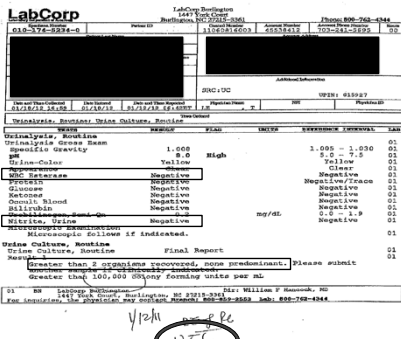
Lopa Shah, MD, Nasdin Mandlik, DO, Payal Kumar, MD, Surjan Andaya, MD, and Pingsong Patmasouvan, MD

Urinary tract infection (UTI) in children is a common diagnosis in general pediatric practice. Because of the increased number of urinary tract infections, it is important to adhere to the AAP It is found that at the a tion, there is at least 70% adherence to the method of ur



- 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
- Dysuria
- 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?



THE RADIOLOGY OF CHRONIC PYELONEPHRITIS

Antimicrobial Prophylaxis for Children with Vesicoureteral I

Antimicrobial Prophylaxis for Children with Vesicoureteral I





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

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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?

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

Revised, 2010

Panel Members:
 Craig A. Peters, M.D., Chair
 Steven J. Shoup, M.D., Vice-Chair
 Billy S. Arant, Jr., M.D.
 Hillary L. Goops, M.D.
 Jack S. Elder, M.D., Facilitator
 R. Guy Hubbard, M.D.
 Antonio E. Krovury, M.D.
 Armando J. Lorenzo, M.D.
 Hans G. Pohl, M.D.
 Ellen Shapiro, M.D.
 Warren T. Snodgrass, M.D.


Consultants:
 Miryza Diaz, Ph.D.
 Linda Whetter, D.V.M., Ph.D.
 Suzanne Papp, M.B.A.

AUA Staff:
 Hedy Hubbard, Ph.D., M.P.H.
 Michael Fomer
 Corinna James, M.L.S.
 Kadatu Kebe
 Aziz Khan, M.H.S.
 Merris Zuckerman, M.A.

American Urological Association
Education and Research, Inc.

Bladder and Bowel Dysfunction (BBD): Etiology

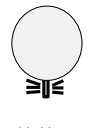
- **Holder**
 - Too busy to go
 - Hurts to go
- **Unstable bladder (Urge syndrome)**
 - Immature bladder; always creating an urge to void
 - Resisted with toilet training
- **“Lazy” bladder**
 - Inadequate emptying; over-flow wetting, infections



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Dysfunctional Voiding – Bladder and Bowel Dysfunction (BBD)

Filling





Low bladder pressure, sphincter active

Balanced Voiding



High Pressure, unbalanced voiding



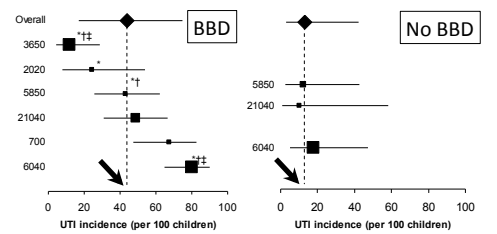


Voiding inhibited by sphincter contraction during bladder contractions

Incomplete emptying due to sphincter contraction during voiding

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UTI incidence with CAP: Impact of Bladder and Bowel Dysfunction

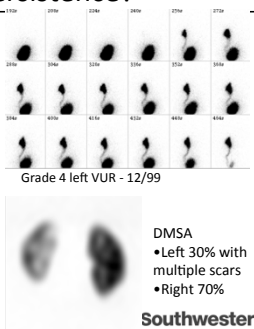


43% incidence if BBD present vs. 12% if no BBD

AUA Reflux Guidelines 2010
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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



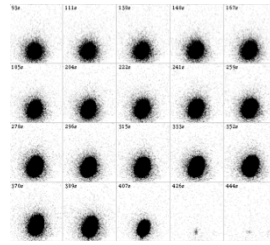
Grade 4 left VUR - 12/99


DMSA
 • Left 30% with multiple scars
 • Right 70%

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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




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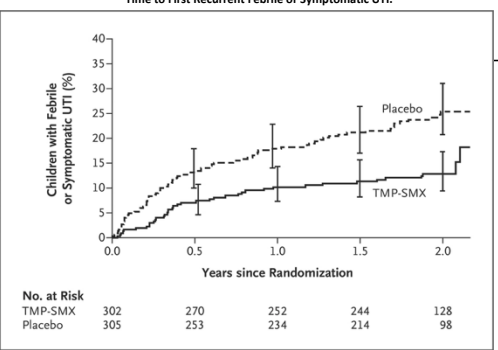
RIVUR

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


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Time to First Recurrent Febrile or Symptomatic UTI.

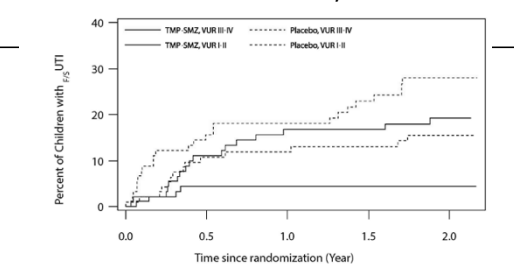


No. at Risk	0.0	0.5	1.0	1.5	2.0
TMP-SMX	302	270	252	244	128
Placebo	305	253	234	214	98


The RIVUR Trial Investigators. N Engl J Med 2014. DOI: 10.1056/NEJMoa1401811

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Children Under 2 years




No. at Risk	0.0	0.5	1.0	1.5	2.0
TMP-SMX, VUR III-IV	93	79	73	71	36
Placebo, VUR III-IV	91	73	68	62	26
TMP-SMX, VUR I-II	91	82	78	77	40
Placebo, VUR I-II	94	81	77	72	34

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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

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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?

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Is this a Real UTI?

LabCorp
118-378-8374
11841503
11831119

2 year old uncircumcised boy
• Dysuria
• Fever to 102
• Fussy but taking PO well

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MT

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

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Grade 3 Reflux

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Reflux and Risk of UTI

	Low	High
Grade	I II III IV V	
Age	School Age Toddler Infant	
BBD	Mild Moderate Severe	
Infections	None Few Recurrent	
Scarring	None Moderate Severe	

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Reflux and Risk of UTI

	Low	High
Grade	I II III IV V	
Age	School Age Toddler Infant	
BBD	Mild Moderate Severe	
Infections	None Few Recurrent	
Scarring	None Moderate Severe	

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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

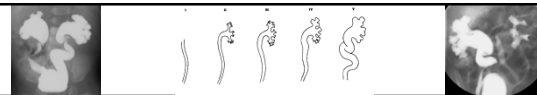


Seeing the Trees and the Forest



Summary

- 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

