

Febrile Urinary Tract Infections in Infants and Children

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Special thanks to **Thomas B. Newman, MD, MPH**, Professor of Epidemiology and Biostatistics and Pediatrics at University of California, San Francisco and to **Ken Roberts, MD**, Chair of the AAP Subcommittee on Urinary Tract Infection and Lead Author of UTI guidelines for sharing their data and slides.

Objectives

- Review latest AAP guidelines on diagnosis and treatment of UTI.
- Discuss changes to imaging recommendations after first UTI.
- Review evidence around antibiotic prophylaxis for prevention of UTI.

ED Case Presentation

- 9 month-old female with no PMH.
- Fever to 102° F x 2 days
- Increased fussiness & decreased PO intake, but no other symptoms.
- VS: T 104° F, HR 170, RR 20, BP 85/50
- Well-hydrated, fussy but consolable, no localizing source of fever.

Prevalence of UTI (meta-analysis)

- 5-7% prevalence in infants presenting with fever
 - Varies by age, gender, race and circumcision status
 - Prevalence of UTI in febrile females
 - aged 0-3 months 7.5%
 - aged 3-6 months 5.7%
 - aged 6-12 months 8.3%
 - aged > 12 months 2.1%
 - Prevalence of UTI in febrile male infants
 - Circumcised males: 2.3% < 3 mos; 0.3% 6-12 mos.
 - Uncircumcised males: 20.1% < 3 mos; 7.3% 6-12 mos.
 - UTI in 8% infants of white race vs. 4.7% infants of black race

Does this child have a UTI?

- Increased likelihood of UTI with:
 - Fever $> 40^{\circ}\text{C}$ (104°F)
 - Suprapubic tenderness
 - Lack of circumcision in male infants
 - Combinations of findings (fever $> 39^{\circ}\text{C}$ for > 24 hours, white race, h/o UTI, no other apparent source).

Probability of UTI Among Febrile Infant Girls and Infant Boys According to Number of Findings Present.

Individual Risk Factors: Girls
White race Age < 12 mo Temperature $\geq 39^{\circ}\text{C}$ Fever ≥ 2 d Absence of another source of infection

Probability of UTI	No. of Factors Present
$\leq 1\%$	No more than 1
$\leq 2\%$	No more than 2

Individual Risk Factors: Boys
Nonblack race Temperature $\geq 39^{\circ}\text{C}$ Fever > 24 h Absence of another source of infection

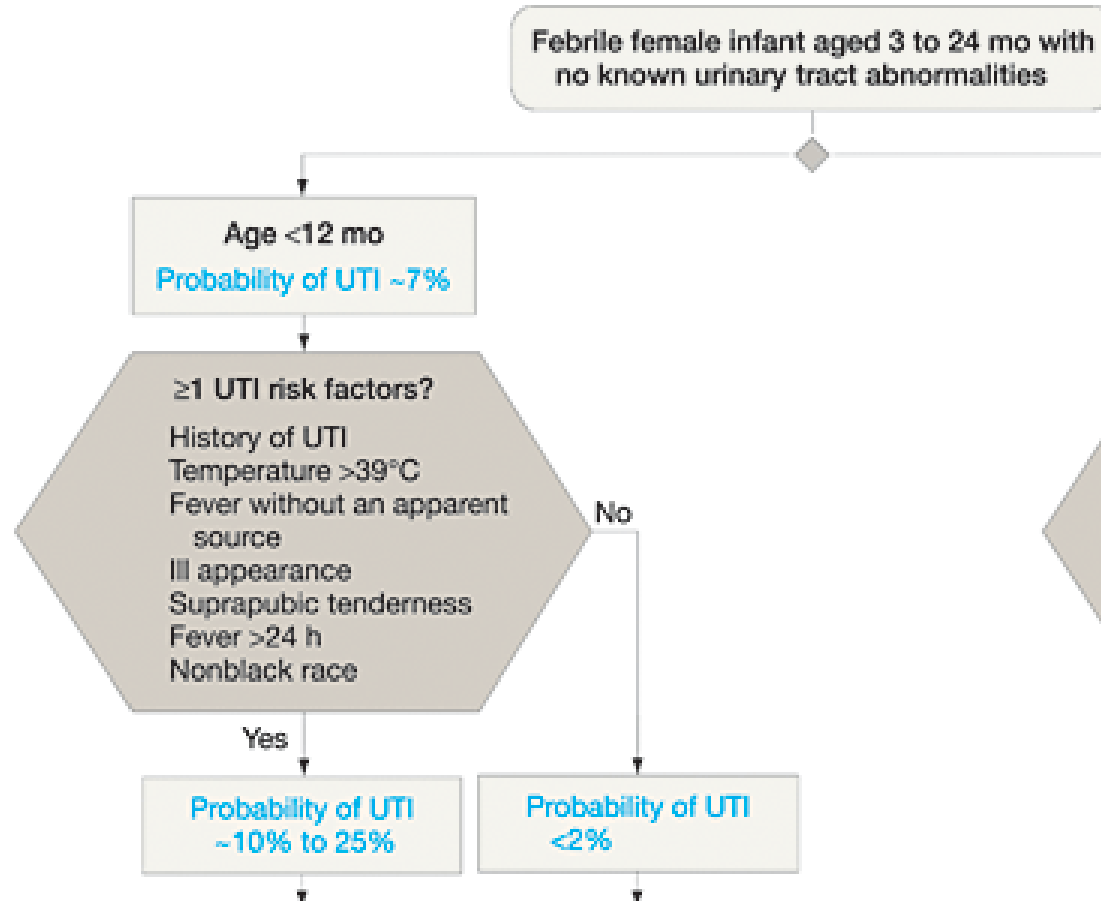
Probability of UTI	No. of Factors Present	
	Uncircumcised	Circumcised
$\leq 1\%$	a	No more than 2
$\leq 2\%$	None	No more than 3

Pediatrics 2011;128:595-610
Pediatrics 2016;138(6):e20163026

Back to case

- Female
- < 12 months
- White race
- Fever > 39
- Fever \geq 2 days
- No other apparent source

Diagnostic Algorithm for Febrile Female Infants Aged 3 to 24 Months Suspected of Having a UTI



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

2011 AAP recommendations:

- In *toxic* infants with fever, obtain urine prior to giving abx.
 - Bag is worthless in this situation
 - Suprapubic aspiration is gold standard, *but...*
 - Catheterization has sensitivity and specificity approaching SPA

Pediatrics 2011;128:595-610

Pediatrics 2016;138(6):e20163026

Options

- A. If a *well-appearing* infant has low likelihood of UTI, follow clinically.
- B. If not low-likelihood, obtain urine specimen:
 1. By SPA or catheterization
 2. By bag
 - If completely negative urinalysis, monitor clinically
 - If urinalysis suspicious, obtain SPA or cath

Case presentation (continued)

- Given relatively high pretest probability of UTI, you decide to catheterize.
- On urinalysis:
 - SG 1.010
 - pH 6.5,
 - 2+ LE
 - Positive nitrite
 - 10 wbc/hpf
 - 5-50 bacteria/hpf
 - otherwise negative.

Components of urinalysis

- **Leukocyte esterase:** surrogate marker for white blood cells in the urine
- **Nitrite:** converted from dietary nitrates by GNR in the urine
 - Not all urine pathogens perform this reaction
 - Takes 4 hours
- **Gram stain of urine:** on *unspun* urine presence of bacteria correlates with colony counts $> 50,000$
- **Pyuria:** >5 wbcs/hpf on centrifuged urine ($10/\text{mm}^3$ on unspun urine)

Sensitivity and Specificity of Urinalysis

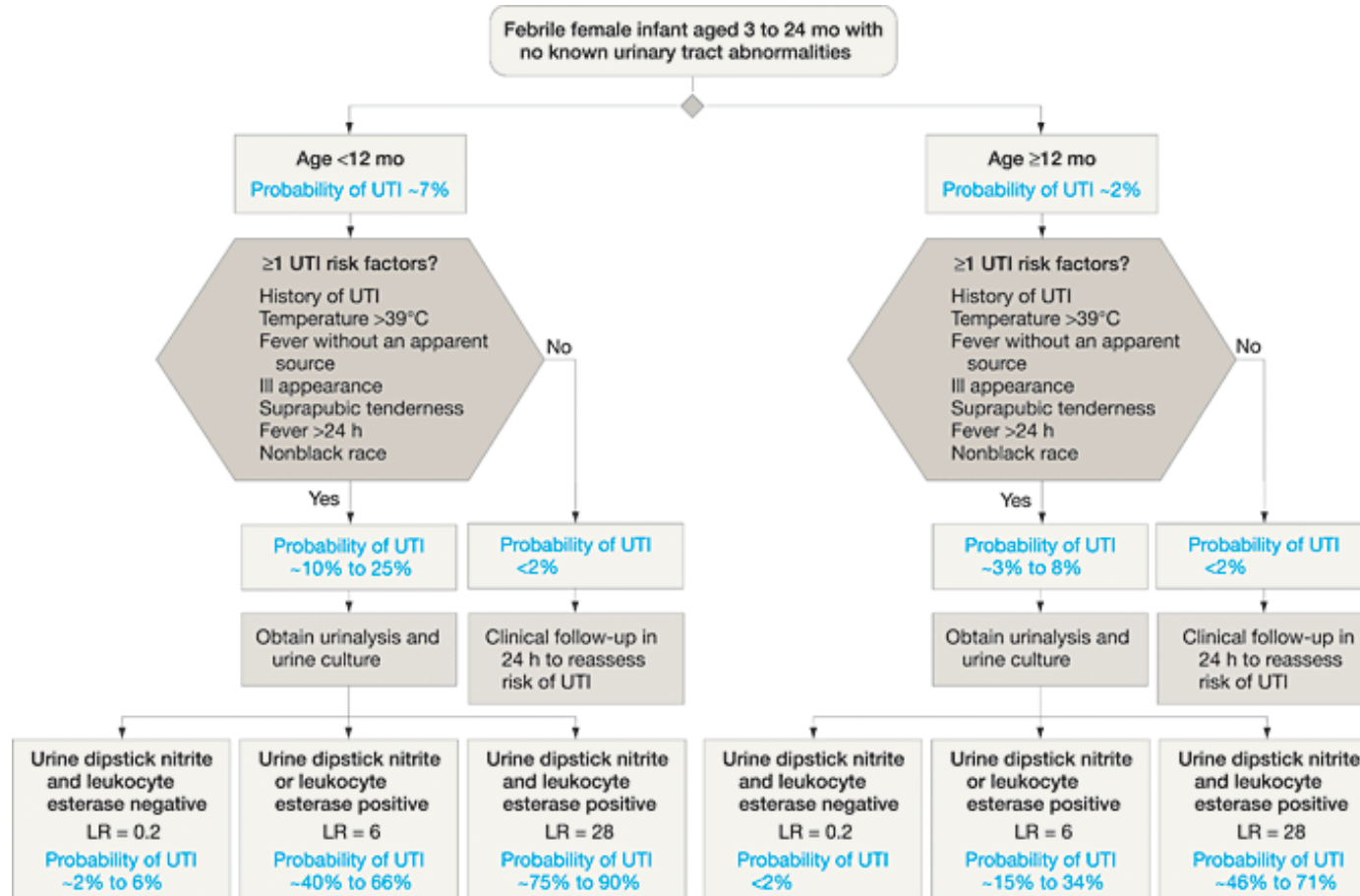
- Gram stain (bacteria) in uncentrifuged urine:
 - Sensitivity: 93%, Specificity: 95%
- Urine dipstick:
 - Sensitivity 88% for LE or nitrite
 - Specificity 96% for LE and nitrite
- Pyuria:
 - Sensitivity 73%
 - Specificity 79% for centrifuged samples, 89% for uncentrifuged samples.

Likelihood ratios for UA in febrile infants (for Positive Urine Culture)

	LR +	LR -
Leukocyte esterase	5.3	0.24
Nitrite	20.0	0.61
>5 WBC/HPF	4.2	0.21
Bacteria on unspun urine	4.6	0.10

Slide adapted from T. Newman, "Diagnosis and Management of Urinary Tract Infections in Infants and Children", 2010.

Diagnostic Algorithm for Febrile Female Infants Aged 3 to 24 Months Suspected of Having a UTI



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<https://jamaevidence.mhmedical.com/calculator.aspx?calc=142839>

UTI Calc

- Calculator for estimating probability of UTI in young febrile children
- Based on chart review of 2070 children in Pittsburgh.
- Incorporates clinical data
 - Suggests UA for probability $>2\%$
- Incorporates UA results
 - Suggests treatment for probability $>5\%$
- <https://uticalc.pitt.edu/>

2011 AAP guidelines

- To diagnose UTI, must have *both*
 - Urinalysis that suggests infection
 - AND $>50,000$ colonies of bacteria on culture
- Distinguishes asymptomatic bacteriuria and contaminants from febrile UTI

Case presentation (continued)

- You decide to treat empirically for UTI.
- Your patient is less fussy after receiving Tylenol for fever.
- Her temperature and HR have normalized.
- She has breastfed well x 2.
- She has voided twice.

How are you going to treat her?

Choice of antibiotics

- E. Coli susceptibilities at Duke:
 - ~50% resistant to ampicillin
 - Increasing resistance to TMP/SMX (81% susceptible in 2000, 77% susceptible in 2015).
 - Susceptibility to 3rd generation cephalosporins > 90%.
 - Susceptibility to gentamicin >90%.

Duration of Therapy

- 7-10 days comparable to 14 days
- Single dose or 1-day therapy not comparable with 7-10 days.
- ***Most children with febrile UTI have nuclear scan evidence of pyelonephritis and therefore probably warrant a longer course of antibiotics.***
- RCT underway (SCOUT study) comparing 5 days to 10 days for confirmed UTI.
<https://clinicaltrials.gov/ct2/show/NCT01595529>

Evidence for Oral therapy

- Prospective, multi-center, randomized trial comparing IV vs. PO antibiotics for 1st febrile UTI in children 1-24 months
- Completed between 1992 –1997
- 306 children randomized to either
 - 14 days of oral cefixime (double dose on day one)
 - Or initial IV cefotaxime for 3 days followed by oral cefixime for 11 days

Hoberman A, et al. *Pediatrics* 1999;104:79-86

Evidence for Oral Therapy

TABLE 4. Clinical Course, Incidence, and Extent of Renal Scarring at 6 Months According to Mode of Therapy and Degree of VUR

Outcomes	Oral Therapy (n = 153)	Intravenous Therapy (n = 153)	P
Defervescence, h Mean (SD)	24.7 (23.2)	23.9 (23.3)	.76
Reinfection, n (%)			
None	132 (86.3)	134 (87.6)	
Symptomatic (UTI)	7 (4.6)	11 (7.2)	.28
Asymptomatic (ABU)	1 (0.7)	2 (1.3)	
Lost to follow-up	13 (8.5)	6 (3.9)	
Outcome DMSA renal scan			
Time performance, mo Mean (SD)	6.8 (1.5)	6.9 (1.9)	.70
Normal, n (%)	117 (76.5)	129 (84.3)	
Renal scarring, n (%)	15 (9.8)	11 (7.2)	.21
Not obtained, n (%)	21 (13.7)	13 (8.5)	
Incidence			.18
Extent			.41
Mean			
Scarring			
No VUR			
Grade 1			
Grade 2			
Grade 3			.37
Grade 4			
Grade 5			

Mean costs:
 \$1473 for children treated orally
 \$3577 for children treated IV

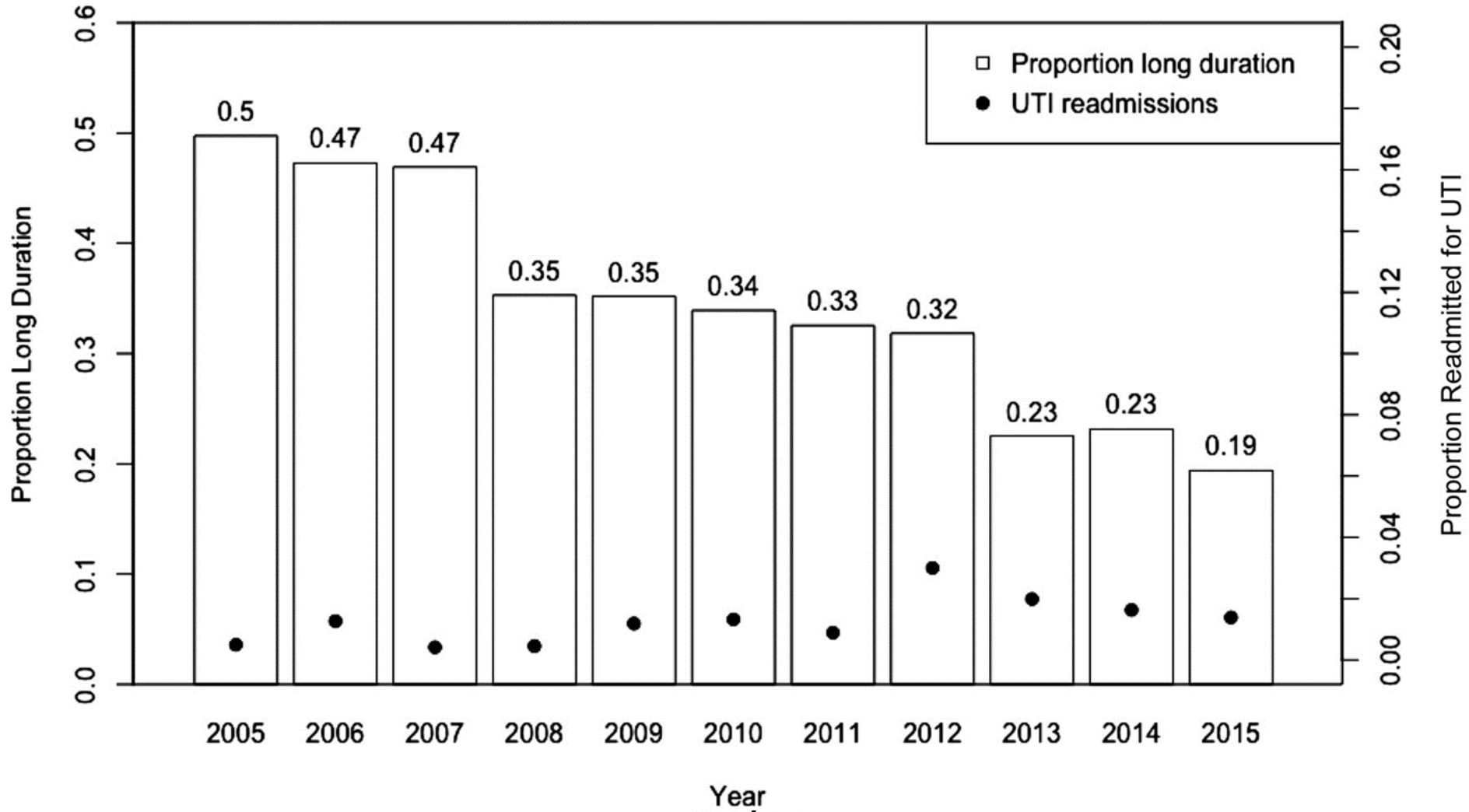
2011 AAP recommendations

- *Initiating treatment orally or parentally is equally efficacious.*
- If toxic or unable to take PO, give parenteral abx and hospitalize.
- Consider local susceptibility patterns and prior abx exposure.
- 7-14 days duration

Pediatrics 2011;128:595-610

Pediatrics 2016;138(6):e20163026

What about infants < 2 months?



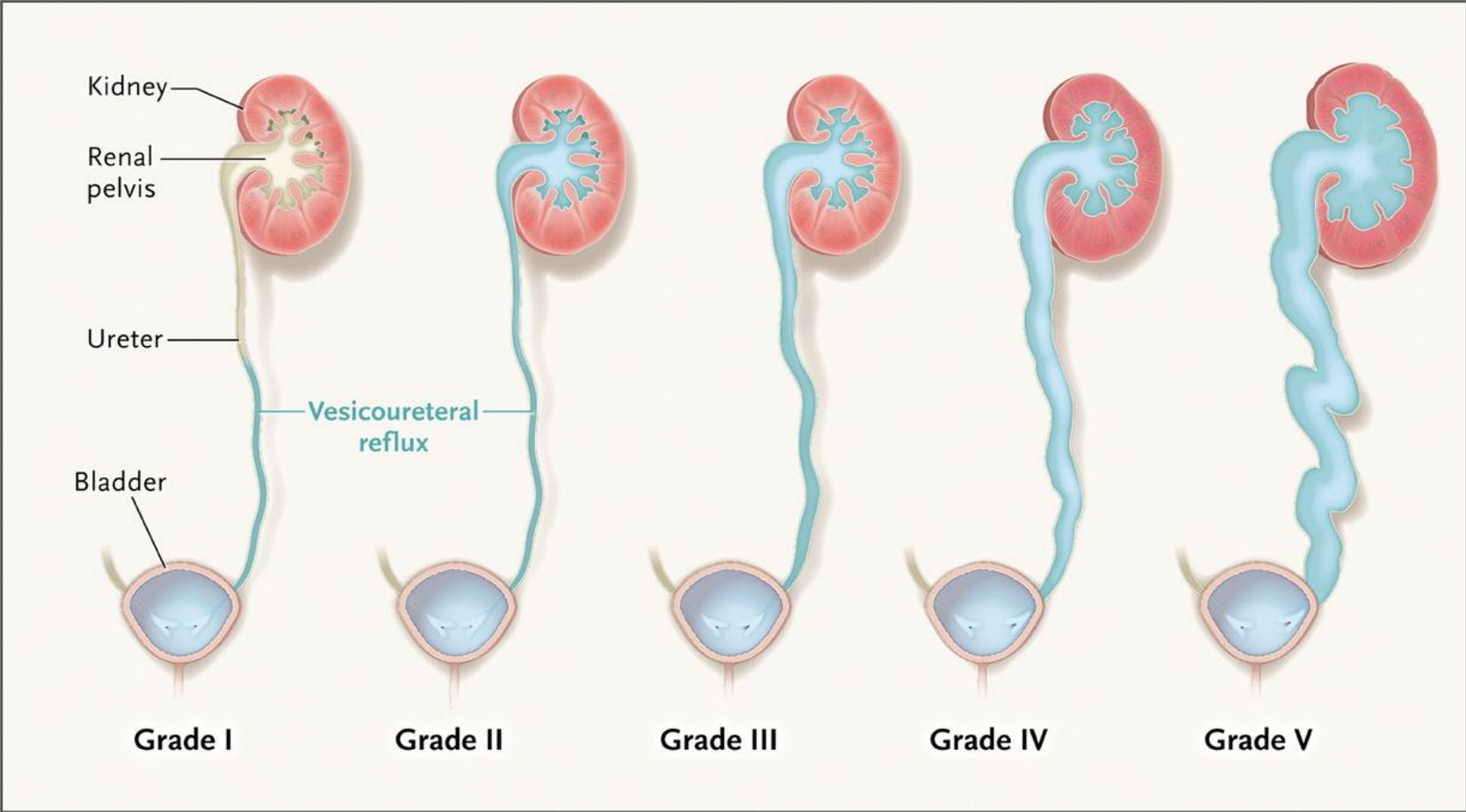
Case presentation (continued)

- The patient is given the first dose of oral cefixime in the ED, but vomits and refuses further PO.
- She is admitted and treated with IV ceftriaxone for 48 hours, defervesces and begins to take better PO.
- Urine culture grows >100,000 colonies of E. coli resistant to ampicillin, but susceptible to TMP/SMX.
- Plan for discharge on oral TMP/SMX to complete 10-day course
- What do you do about imaging?

2011 AAP Guidelines

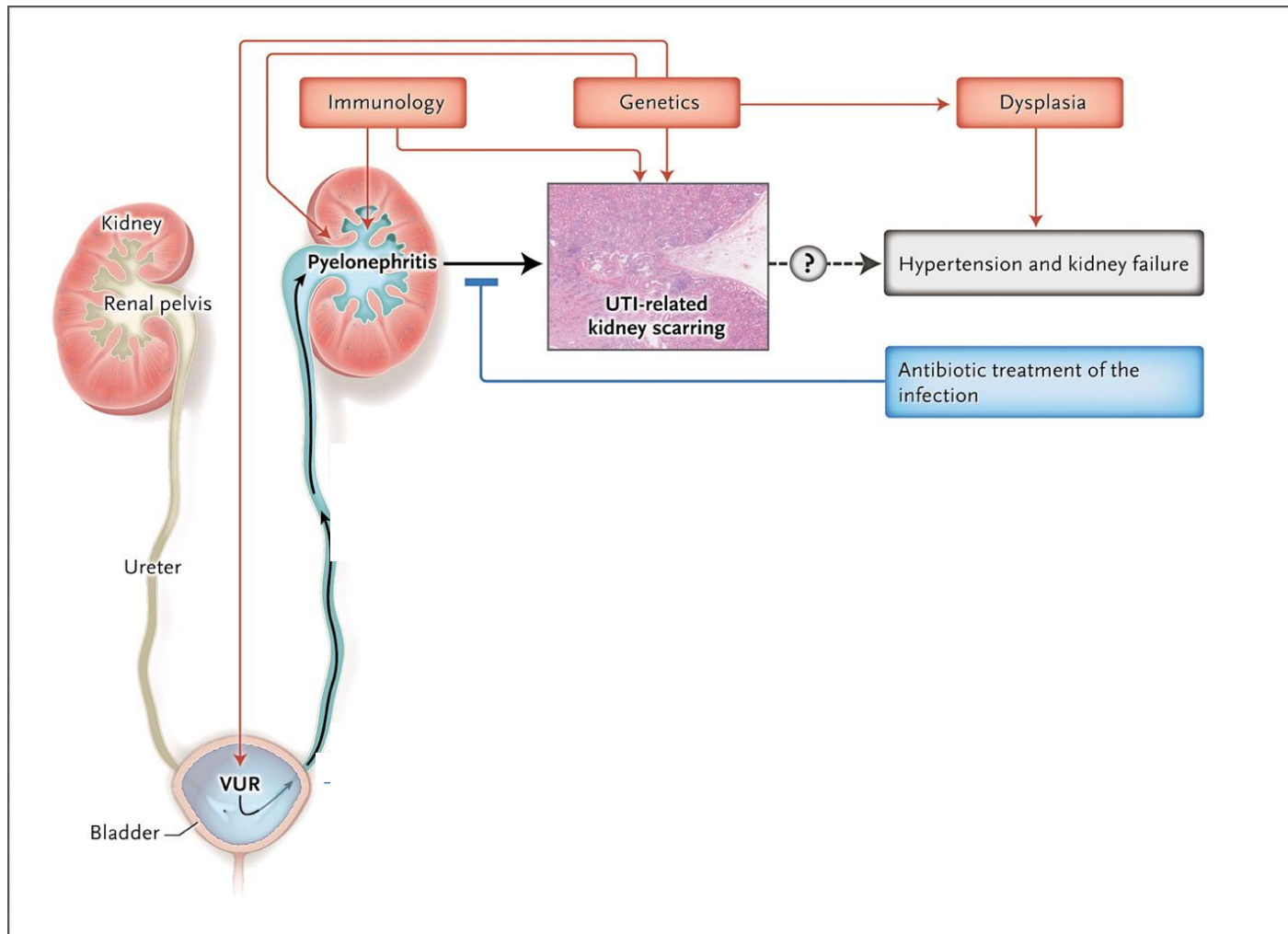
- Febrile infants with UTI should undergo renal and bladder ultrasound.
- VCUG should not be performed routinely after first febrile UTI
 - Perform VCUG if RUS abnormal
 - Perform VCUG for recurrent UTI

International Classification of Vesicoureteral Reflux



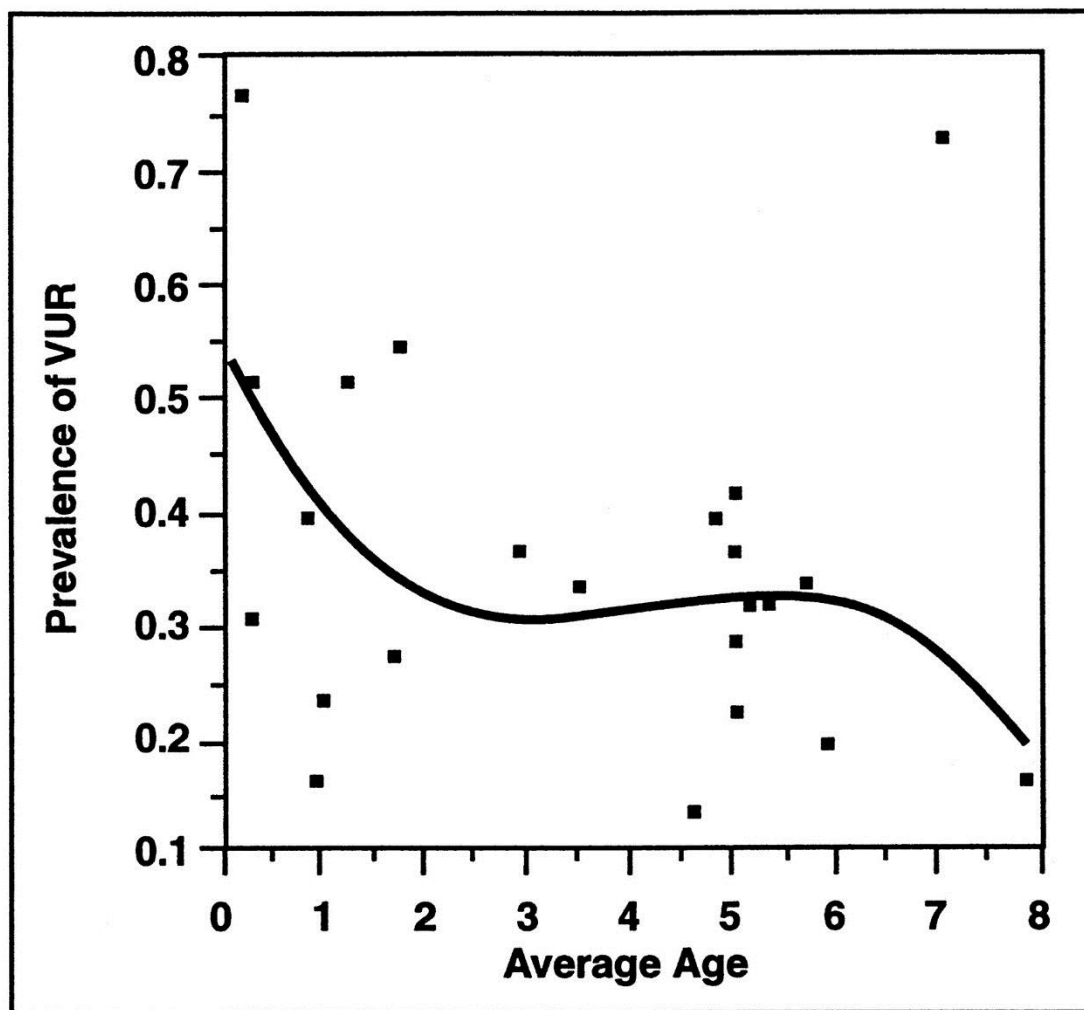
Montini G et al. N Engl J Med 2011;365:239-250

Proposed Pathophysiology of Febrile Urinary Tract Infections and Renal Scarring



Montini G et al. N Engl J Med 2011;365:239-250

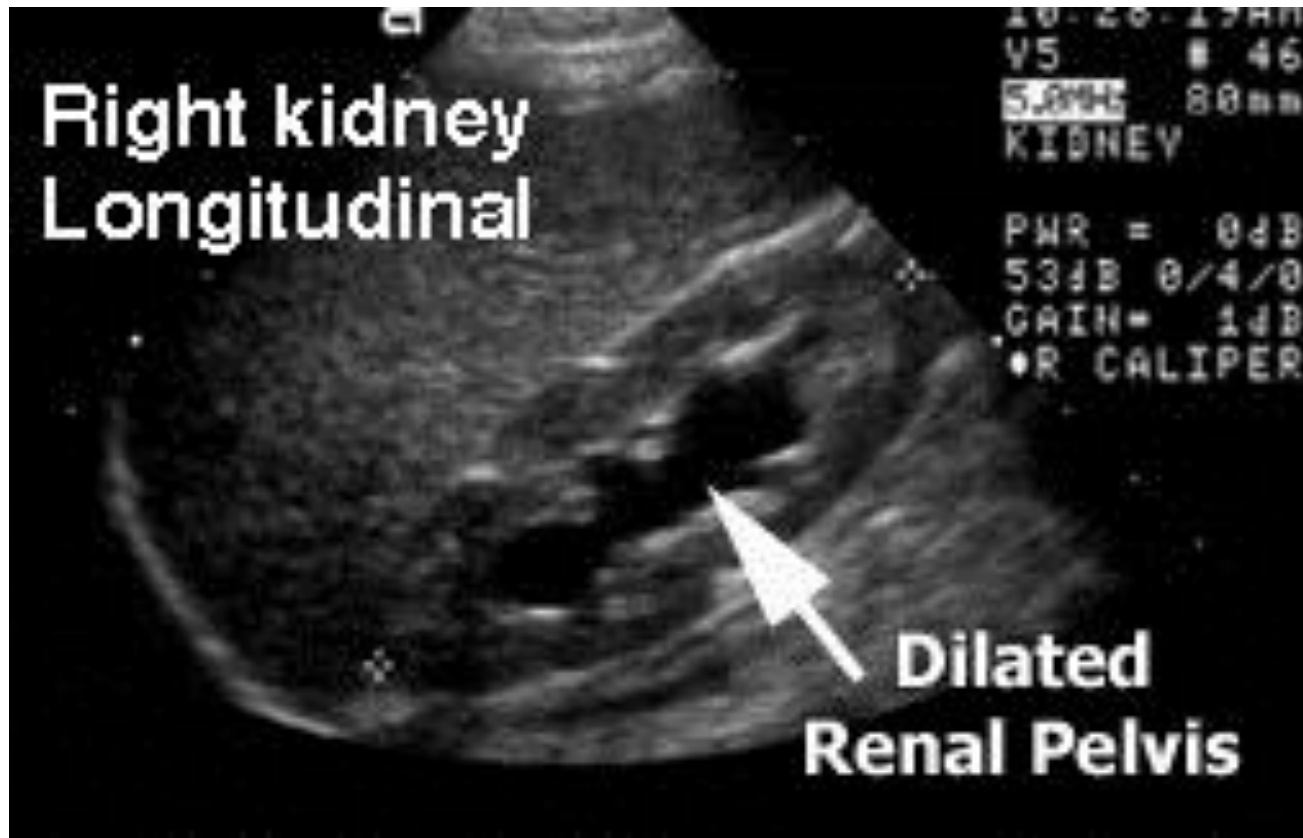
Prevalence of VUR by Age



Committee on Quality Improvement, et al. Pediatrics 1999;103:843-852

PEDIATRICS[®]

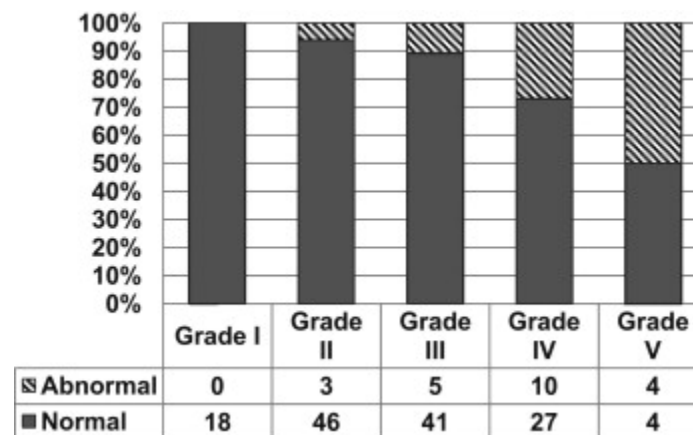
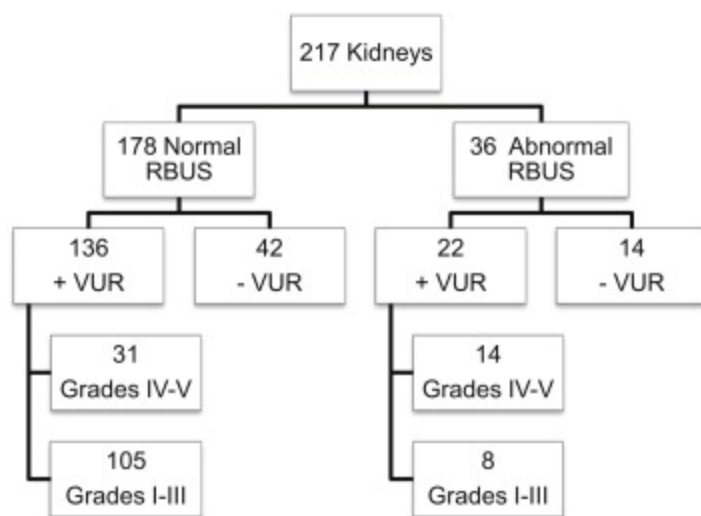
Renal Ultrasound





VCUG showing Grade III reflux on the right and Grade IV reflux on the left.

How good is the RUS at detecting VUR?

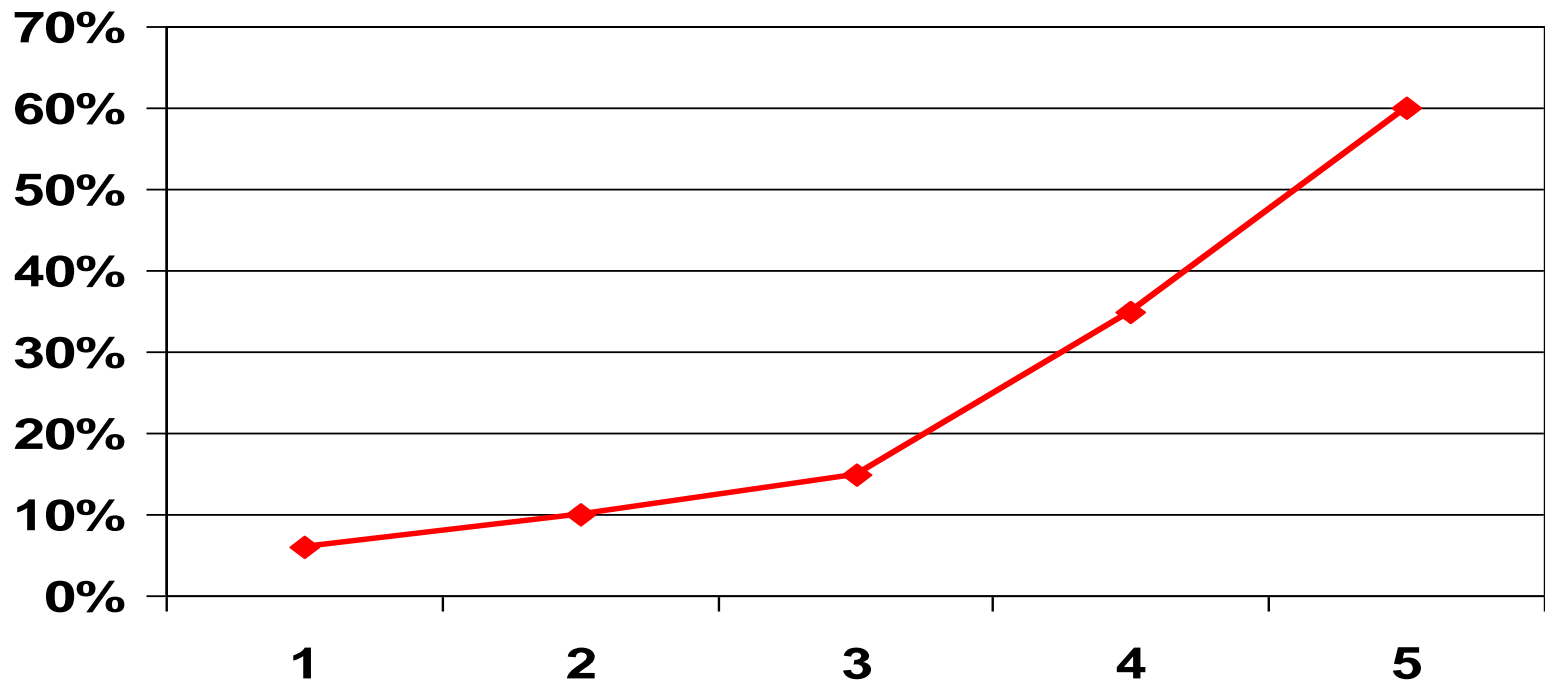


	Gr I-V	Gr II+	Gr III+	Gr IV+	Gr V
Sensitivity	0.16	0.18	0.23	0.36	0.5
NPV	0.25	0.35	0.6	0.83	0.98

VCUG Costs and Risks

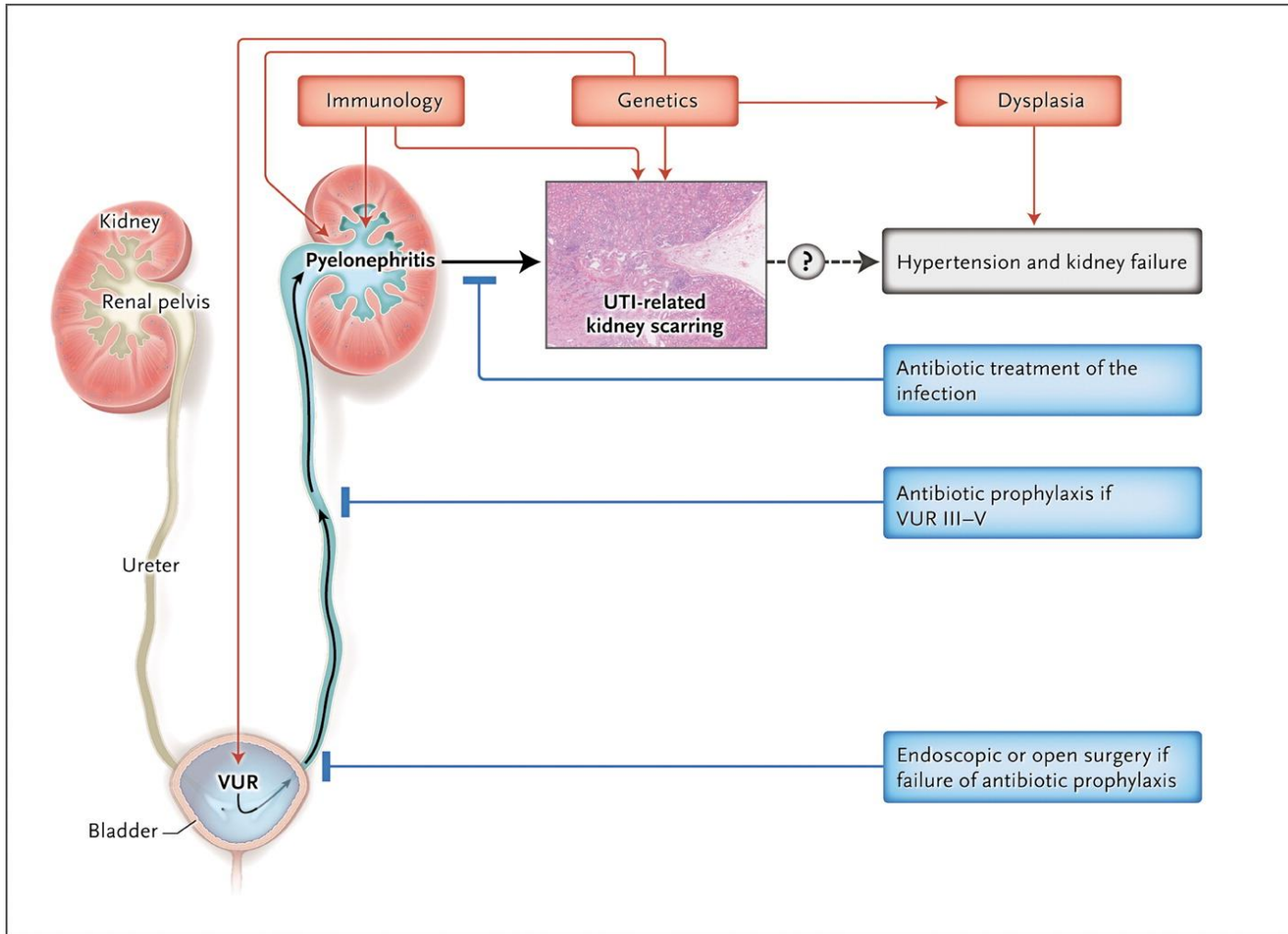
- Charges (DUMC, 2010): \$710.53
- Risk of causing infection ~ 5-10% (Glynn, Ann Radiol 1970;13:283-7; Lohr, Pediatr Infect Dis J. 1994; 13: 812)
- Radiation exposure: 0.8 mSv* (CT = scan 10 mSv)
- Distress/trauma if not sedated
- Risk associated with sedation

Waiting until recurrence...



Risk of Renal Scarring by Number of UTIs

What do we do about VUR if we find it?



Montini G et al. N Engl J Med 2011;365:239-250

RCTs of prophylaxis for UTI prevention

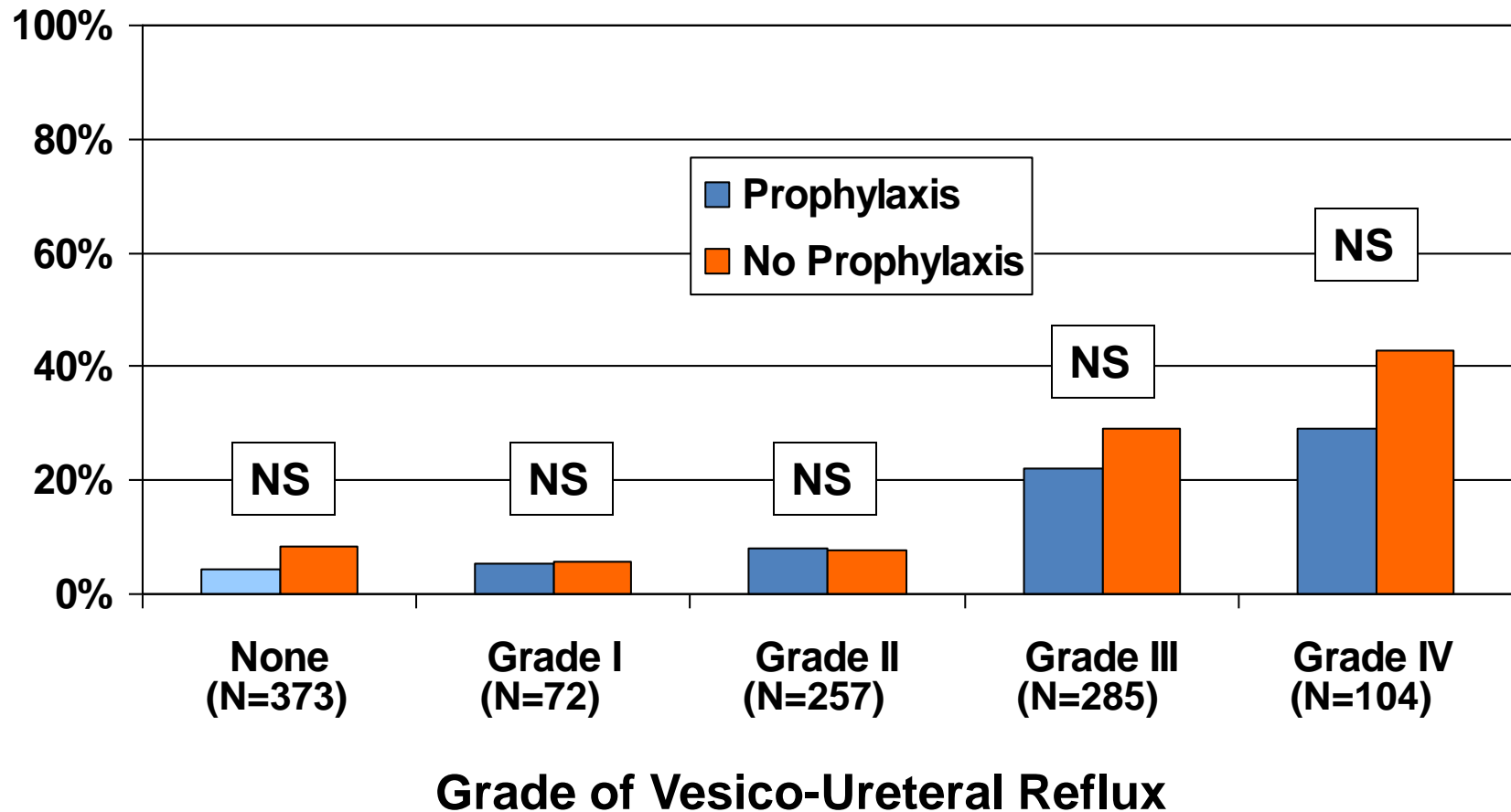
1. Garin E, et al. Pediatrics 2006;117:626-32.
2. Pennesi M, et al. Pediatrics 2008;121:e1489-94.
3. Montini G, et al. Pediatrics 2008;122:1064-71.
4. Roussey-Kesler G, et al. J Urol 2008;179:674-79.
5. Craig J, et al. N Engl J Med 2009;361:1748-59.
6. Brandström P, et al. J Urol 2010;184:286-91.

Meta-analysis of raw data from RCTs comparing UTI recurrence

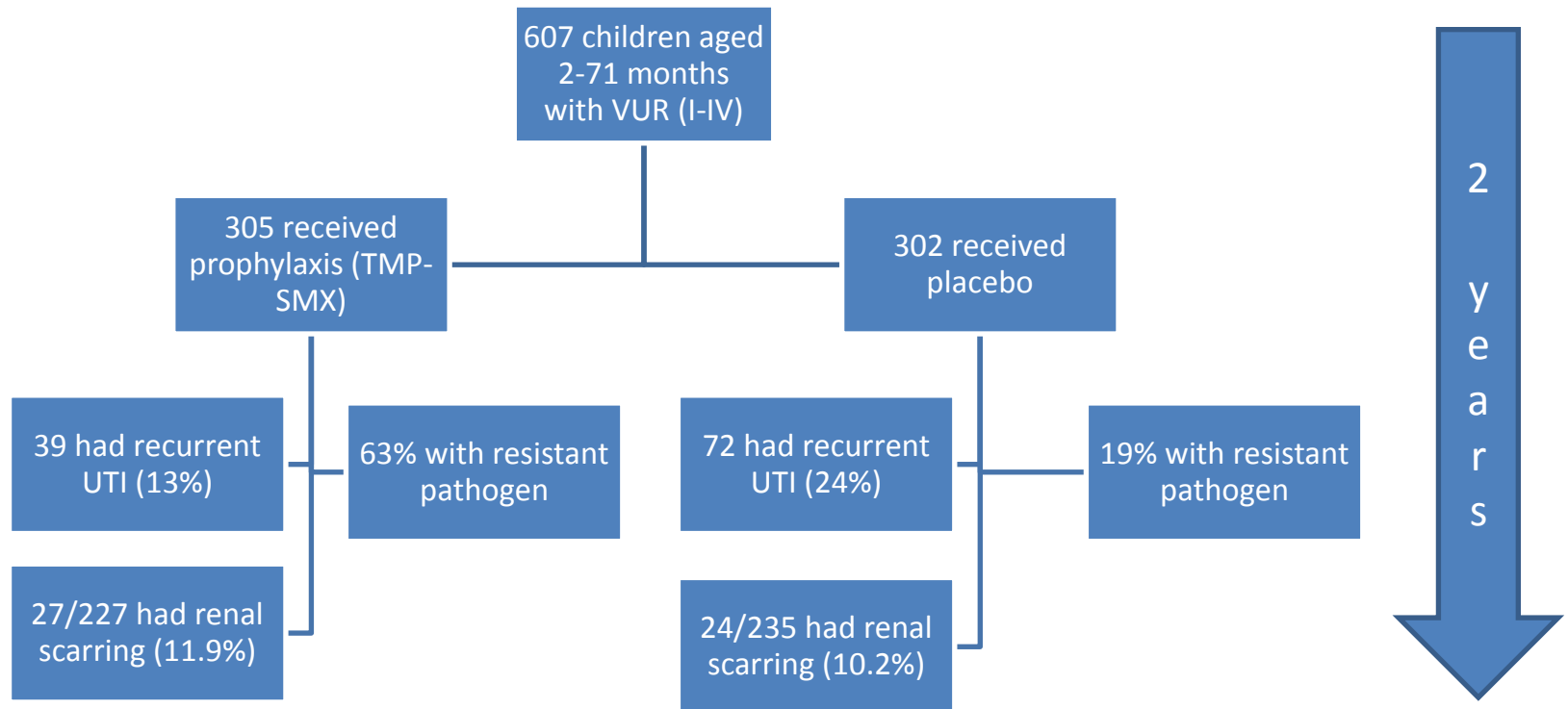
Reflux	N	Prophylaxis	No Prophylaxis	p value
None	373	7 / 210	11 / 163	0.15
Grade I	72	2 / 37	2 / 35	1.00
Grade II	257	11 / 133	10 / 124	0.95
Grade III	285	31 / 140	40 / 145	0.29
Grade IV	104	16 / 55	21 / 49	0.14
	1,091			

Recurrence Rate of Febrile UTI By Grade of Reflux, 1,091 Infants 2-24 Months

Recurrence

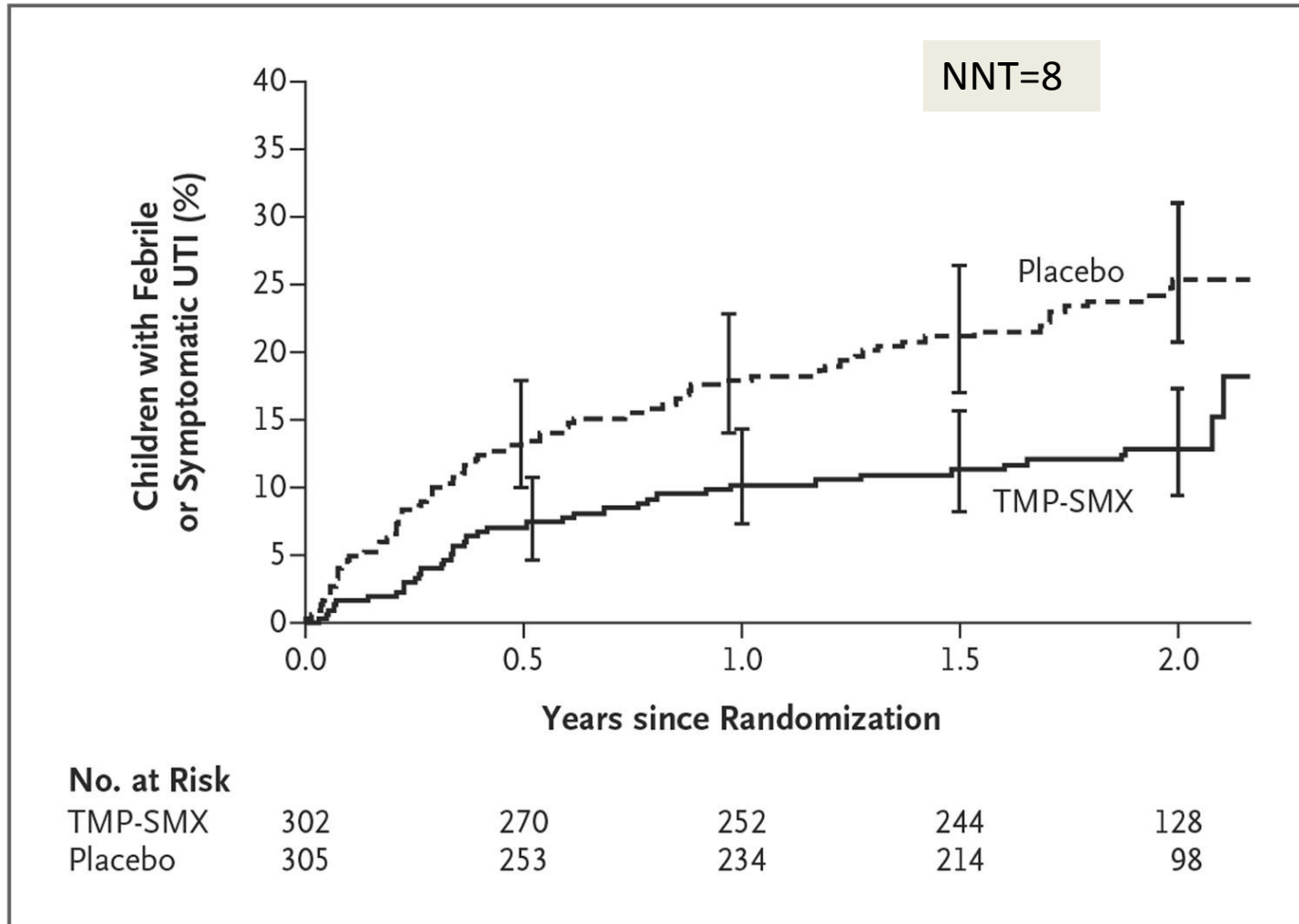


What does the RIVUR study add?



75% reported adherence 75% of the time
85% reported adherence 50% of the time

Time to First Recurrent Febrile or Symptomatic UTI



AAP response to RIVUR

- The findings do not justify subjecting large numbers of infants to VCUG because:
 - The benefit was not significant for those with higher grades of VUR (also true for Craig et al).
 - Prophylaxis did not reduce the number of infants in whom renal scars developed.

Risk stratification for prophylaxis?

LOW

Circumcised Males and Females with VUR Grade I-III
AND
No BBD/Constipation

HIGH

Uncircumcised Males with VUR Grade I-III
± BBD/Constipation
OR
Females with VUR Grade I-III
and BBD/Constipation
OR
Females and Males with VUR Grade IV
± BBD/Constipation

Back to case presentation.

- 9 month-old female with 1st febrile UTI.
- RUS done after completing therapy reveals mild pelviectasis.
- VCUG reveals Gr 1 VUR.
- What do you do?

Conclusions

- Although there are a number of controversial issues, the following remain true:
 1. UTI is a relatively common cause of fever without source in infants and young children.
 2. Urine culture is the diagnostic gold standard, but children with febrile UTI should also have evidence on urinalysis.
 3. Oral treatment can be equivalent to parenteral treatment in non-toxic patients.

Conclusions (continued)

4. The majority of febrile infants with UTI have pyelonephritis; therefore short courses of antibiotics should not be used.
5. Prophylactic antibiotics decrease the risk of recurrent UTI in children with VUR, *but*
 - *They have not been shown to prevent renal scarring*
 - *They lead to antimicrobial resistance*
6. Evaluate promptly for UTI in children with FWS who have a history of prior UTI.