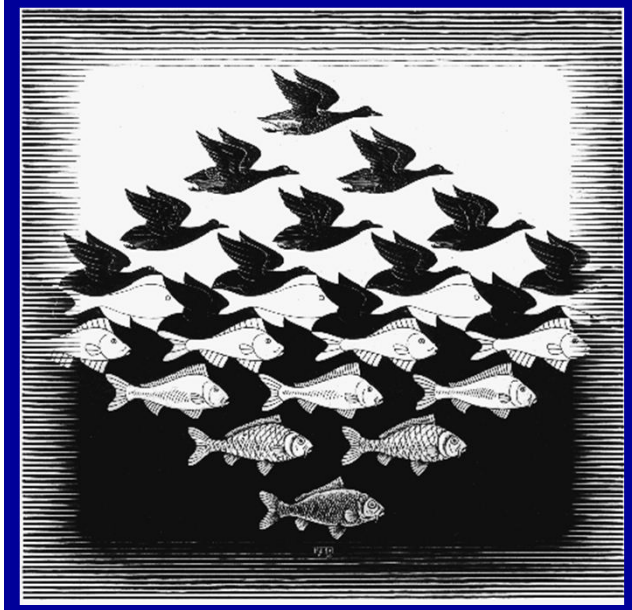
Recurrent Pediatric UTI – Revisited 2013



Medicine changes constantly

PIDSP 21.2.2013

Shai Ashkenazi, MD, MSc

Some aspects of the standard practice of ~40 years are probably not valid and need to be changed

American Academy of Pediatrics

FROM THE AMERICAN ACADEMY OF PEDIATRICS

Pediatrics 9/2011;128:595-610

CLINICAL PRACTICE GUIDELINE

Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months

The NEW ENGLAND JOURNAL of MEDICINE

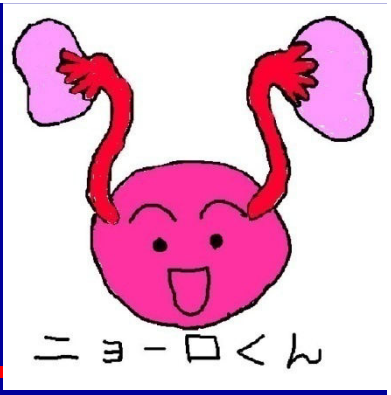
2011;365;239-50

REVIEW ARTICLE

MEDICAL PROGRESS

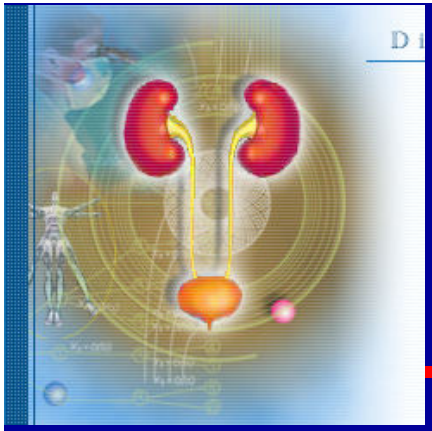
Febrile Urinary Tract Infections in Children

Background



NEJM 2011;365;239-50

- UTI is common in children, affecting
  2% of boys, 8% of girls by 7 years
- Accounting for 7.5% of febrile episodes in < 8w, 5.3% in <1y, 4.1% in < 2y, 1.7% in < 5y
- Recurrence in ~20%
- Post-infectious renal scarring after a APN: 10%-65%
- Diagnosis of APN and prevention of renal scarring – crucial to prevent late complications



Pediatric UTI – Revisited 2013

- Background
- Antimicrobial therapy
- Adjunctive therapies?
- Imaging
- Antimicrobial prophylaxis

The NEW ENGLAND JOURNAL of MEDICINE

2011;365;239-50

Table 1. Antibiotic Treatment of Febrile Urinary Tract Infection.*

Treatment	Dose	Comments
Intravenous		
Cephalosporins		Increasing resistance
Cefotaxime	12.5–45 mg per kg of body weight four times per day	
Ceftazidime	30–50 mg per kg three times per day	Good coverage for pseudomonas
Ceftriaxone	50–75 mg per kg once daily or 25–37.5 mg per kg twice per day	Advantage of once-daily dosing; contraindicated in neonates, especially premature infants
Aminoglycosides		Useful for patients with cephalosporin allergy; nephrotoxic; serum levels must be monitored and dosage adjusted accordingly; single daily dosage supported by meta-analysis[55]
Gentamicin	2–2.5 mg per kg three times per day	
Amikacin	7.5 mg per kg twice per day	
Piperacillin–tazobactam	2–9 months of age: 80 mg of piperacillin and 10 mg of tazobactam per kg three times per day; more than 9 months of age: 100 mg of piperacillin and 12.5 mg of tazobactam per kg three times per day	Broad spectrum of bactericidal activity
Oral		
Trimethoprim–sulfamethoxazole	4 mg per kg twice per day (dose expressed in trimethoprim-equivalent units)	High resistance rates; risk of allergic reaction
Amoxicillin–clavulanic acid	45 mg per kg twice per day (dose expressed in amoxicillin-equivalent units)	Increasing resistance
Cephalosporins		Increasing resistance
Ceftibuten	9 mg per kg once daily	
Cefixime	8 mg per kg once daily	
Ciprofloxacin	10–20 mg per kg twice per day	A second choice for the treatment of complicated urinary tract infections; increasing resistance; increased risk of musculoskeletal adverse events

Oral vs IV/oral therapy of febrile UTI

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
	Cefixime (14d)	Cefotaxime (3 d) + cefixime (11 d)	
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 of renal scarring in children with APN, % (CI)	16.9 (9.1–24.6)	13.6 (6.1–21)	.18
Extent, % renal parenchyma			
Mean (SD)	7.9 (2.7)	8.6 (5.6)	.41
Scarring according to degree of VUR, n (%)			
No VUR	4/75 (5.3)	6/90 (6.7)	
Grade 1 VUR	2/14 (14.3)	2/8 (25)	
Grade 2 VUR	1/19 (5.3)	2/20 (10)	
Grade 3 VUR	5/20 (25)	1/21 (4.8)	.37
Grade 4 VUR	3/4 (75)	0/1 (0)	
Grade 5 VUR	0 (0)	0 (0)	

Abbreviations: VUR, vesicoureteral reflux; UTI, urinary tract infection; APN, acute pyelonephritis; CI, 95% confidence interval; DMSA, ^{99m}Tc–dimercaptosuccinic acid; ABU, asymptomatic bacteriuria.

Indications for initial parenteral antibiotics

- Age < 2 months
- "Toxic" appearance
- Immunocompromised child
- Underlying urinary abnormality
- Inability to take oral medications
- Failure of oral therapy
- Concerns regarding compliance
- Concerns regarding follow-up

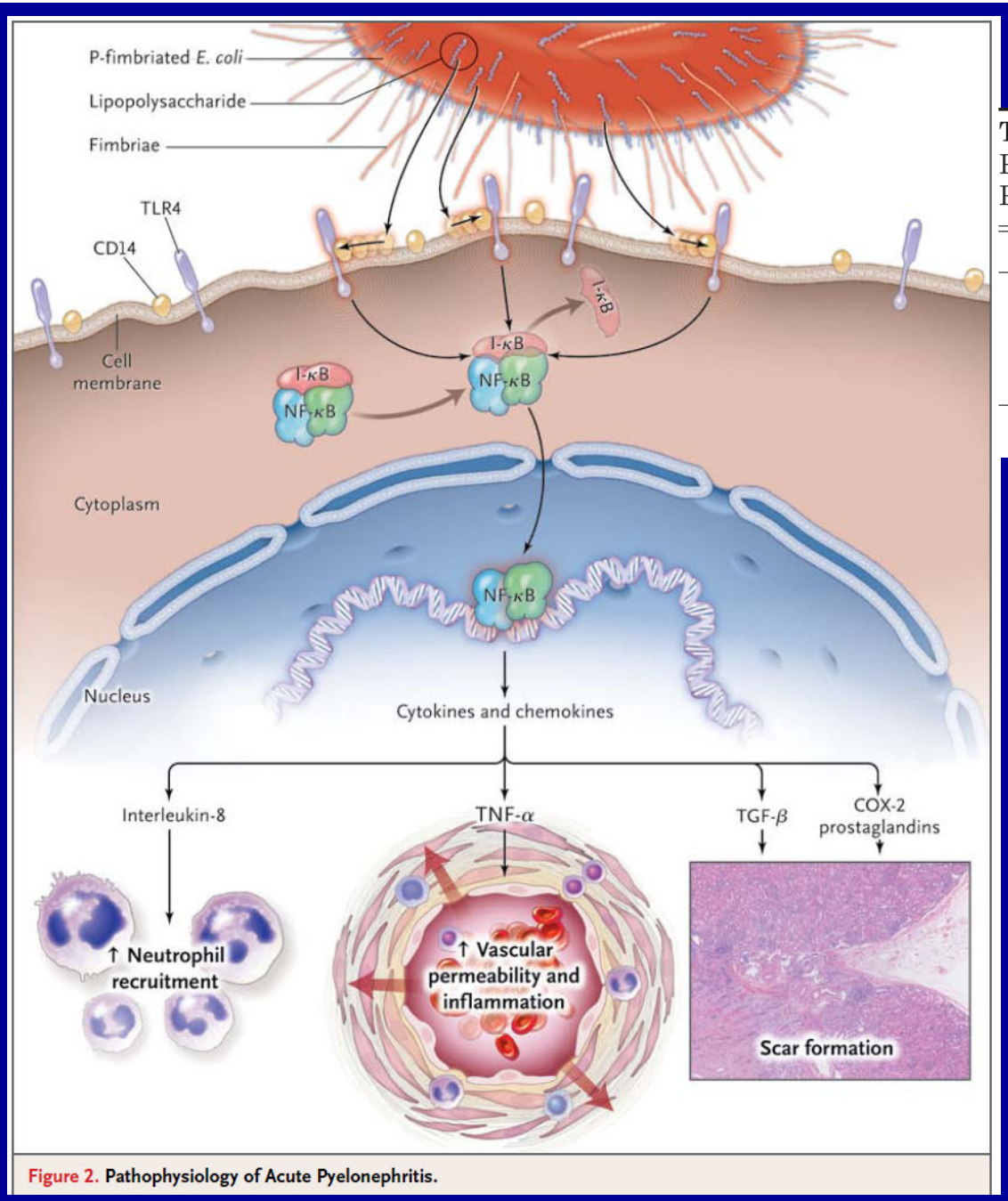


Figure 2. Pathophysiology of Acute Pyelonephritis.

NEJM 2011;365;239-50

TABLE 4. Multiple Linear Regression Analysis for Predicting Renal Scarring in Children After Acute Pyelonephritis

Independent Variable	β*	P
Serum IL-8	0.287	0.026
Urine IL-8	0.509	<0.001
Age	−0.287	0.010
Gender	−0.081	0.488
Reflux grade	0.309	0.006

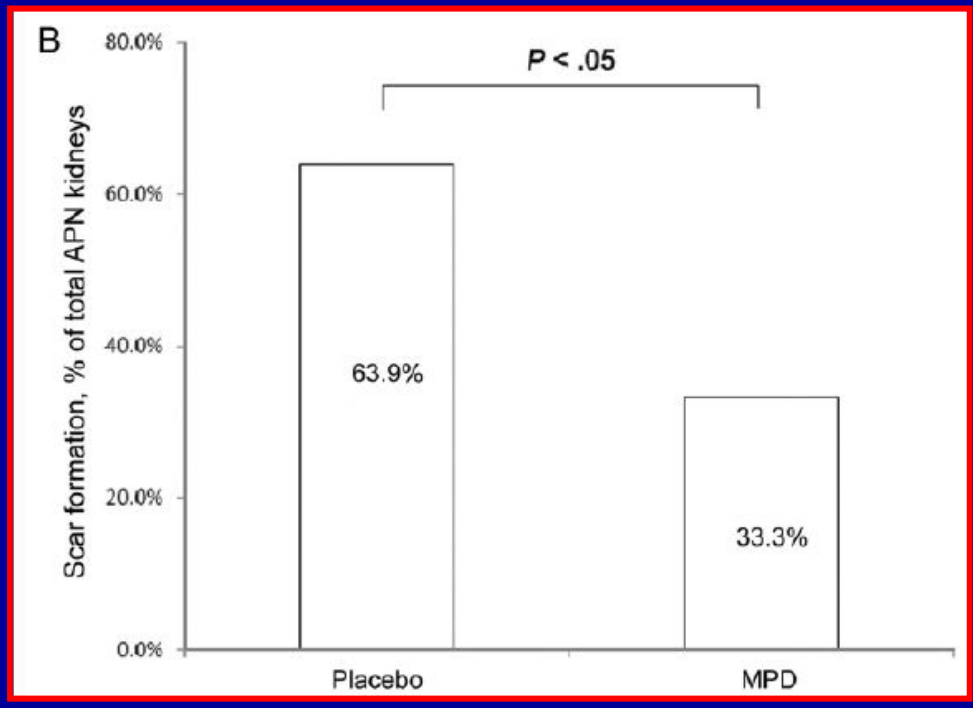
Dependent variable: renal scarring.
*Standardized coefficients.

PIDJ 8/2009

Adjunctive steroids to prevent renal scars

Huang et al, Pediatrics 2011;128:e496

- Steroids decrease urinary cytokines in pediatric APN and renal scarring in animal models.
- 325 children with febrile UTI treated with IV antibiotics
- Randomized to steroids for 3 days or placebo



Eur J Pediatr (2011) 170:347–350
DOI 10.1007/s00431-010-1297-1

ORIGINAL PAPER

European Journal of Pediatrics

The effect of vitamin A on renal damage following acute pyelonephritis in children

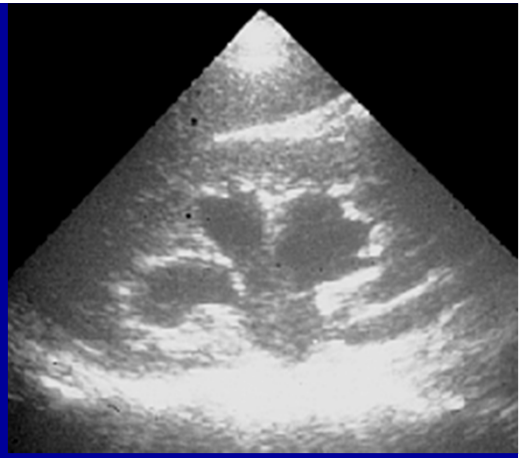
- Vitamin A decreases renal scarring in rats with experimental UTI
- Vitamin A deficiency increases the incidence of UTI
- A single-blind randomized study:
  - 50 children with confirmed APN were treated with ceftriaxone (3 days) – oral cephalexin
  - Randomized to vitamin A (single dose, 25,000 or 50,000 units IM) or no treatment.
  - Renal scarring (3-month DMSA scan): 5/25 (20%) vs 17/25 (68%), p=0.001 (mechanism?)

Imaging in a child with UTI

- Potential findings
- Impact on management
- Recent published guidelines
- Suggested protocol

scan

Renal ultrasound

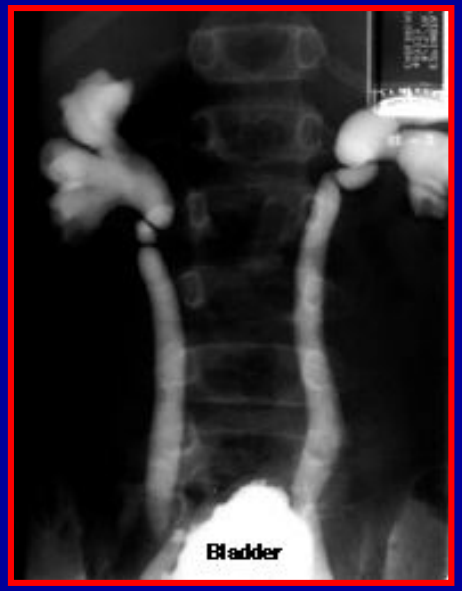


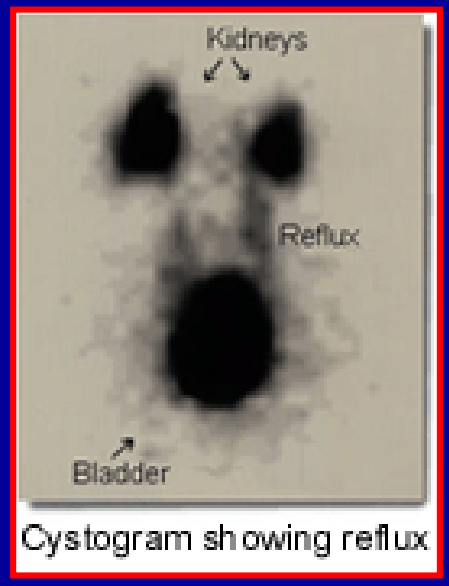
Hydronephrosis

- Simple, non-invasive, radiation-free
- Operator-dependent
- Detects anatomical abnormalities, including dilatation of the collecting system
- Evaluates renal parenchyma, shape and size
- Evaluates voiding dysfunction
- Abnormal results in ~15%; in 1-2% lead to actions

Voiding cystourethrography (VCUG)

- Invasive with radiation exposure: requires bladder catheterization for instillation of radiopaque/radioactive material
- <u>Gold standard for detecting VUR</u>
- 2 types:
  - With radiopaque material
    - Enables the best anatomic imaging and grading of VUR
  - With radioactive material, which is:
    - More sensitive
    - 100 times less radiation
    - Less expensive

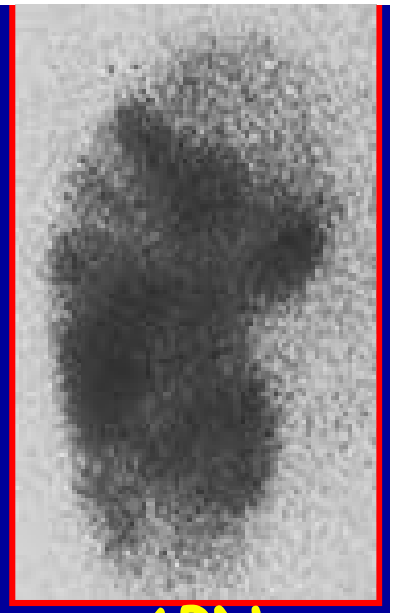




Cystogram showing reflux

DMSA-labeled nuclear scan

- Injected IV and renal uptake is recorded 2-4 hours later
- Areas of PN (in the acute phase) or scar (>6-12m) will present as decreased uptake
- "Less" invasive and lower radiation dose (~1mSv) than VCUG
- Very effective in diagnosis of:
  - APN (sens 86%, spec 91%)
  - Renal scars or renal dysplasia



APN

Renal scar

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 16, 2003 VOL. 348 NO. 3

A. Hoberman et al.

Imaging Studies after a First Febrile Urinary Tract Infection in Young Children

- **Prospective study**
- **309 1-24m children with UTI**
- **US and DMSA scan within 72h**
- **VCUG after 1m**
- **Repeated scan after 6m**

Imaging in a child with UTI

Results

- US had a sensitivity of 10% and a PPV of 40% in detecting VUR
- VUR grade 3-4 was more likely to occur among children with abnormal US (p=0.02)

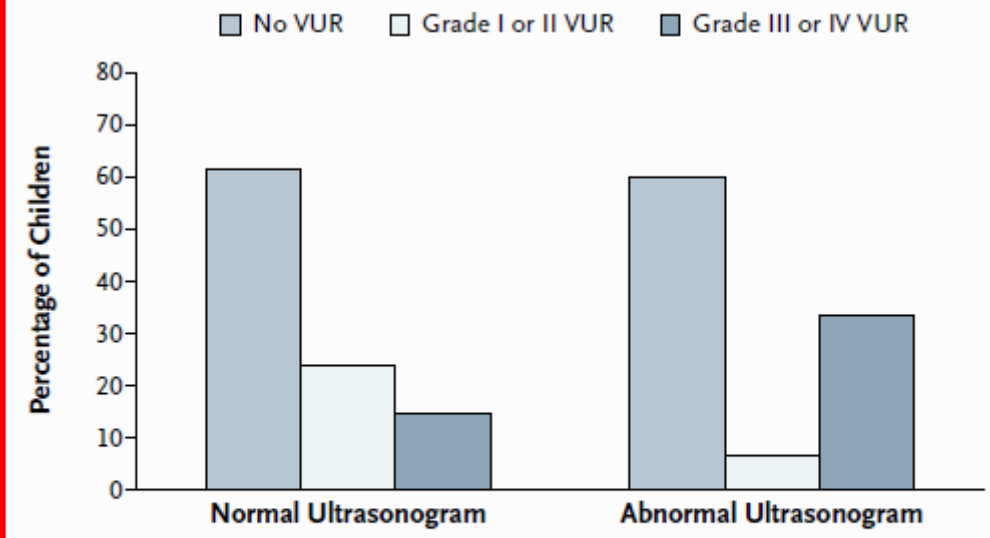
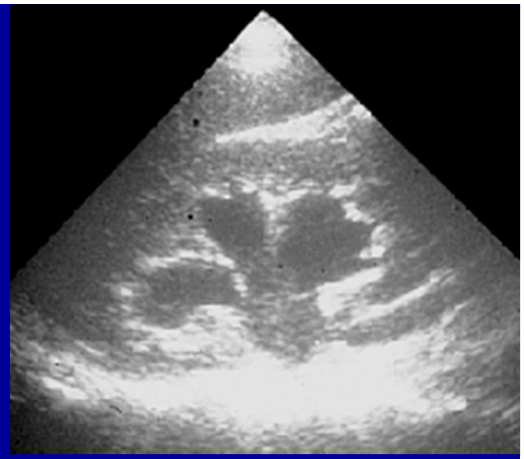


Figure 2. Frequency and Degree of Vesicoureteral Reflux (VUR) According to the Presence or Absence of Evidence of Dilatation of the Urinary Tract on Renal Ultrasonography in Children with a First Urinary Tract Infection.

Conclusion

- "US performed during acute illness is of limited value"

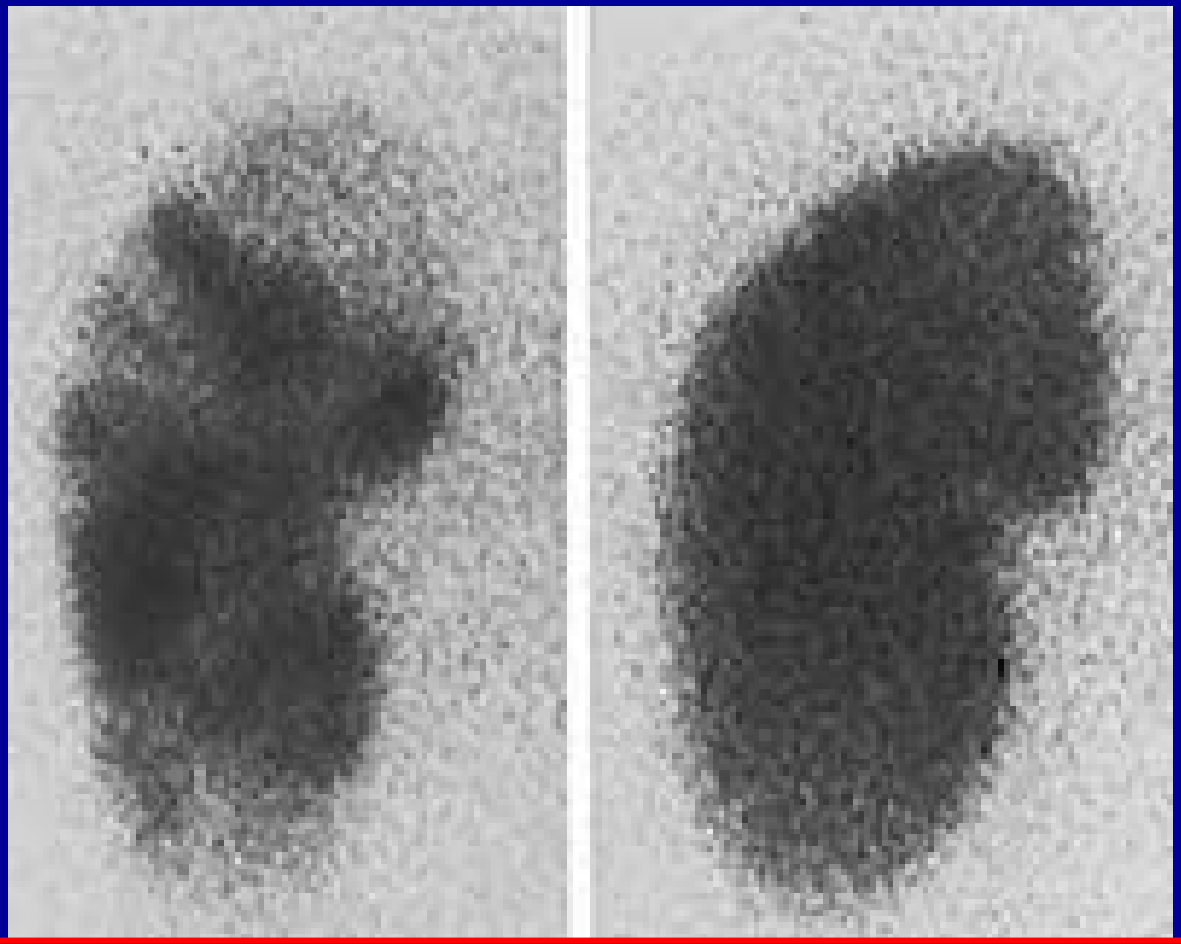
Renal ultrasound



Limitations

- Insensitive to detect VUR, PN or renal scars (doesn't detect VUR directly)
- Most (~70%) anatomical abnormalities can be detected by prenatal US
- False-positive results when performed during acute infection in 2-3%:
  - Transient dilatation of the collecting system (LPS)
  - Edema of the kidneys common during acute infection

A DMSA scan during APN (lt) and after 6 mo (rt) showing complete resolution



The information from a DMSA scan during the acute illness does not influence the treatment decisions

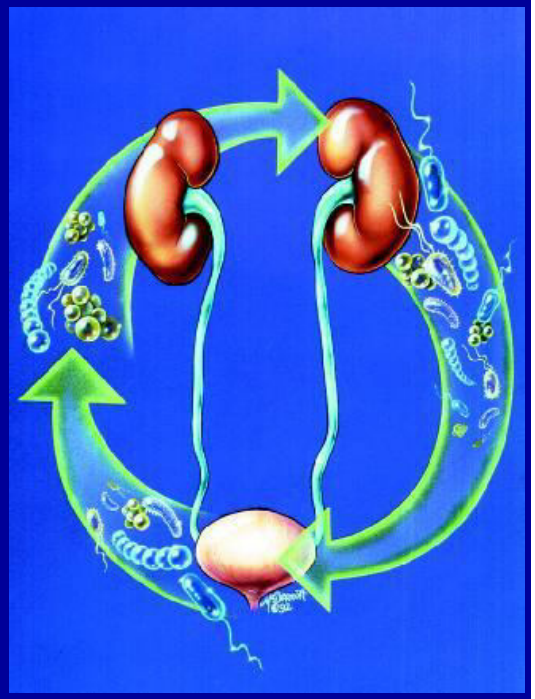
1999 AAP Practice Parameter: The Diagnosis, Treatment, and Evaluation of the Initial UTI in Febrile Infants and Young Children

- Infants and children 2 mo-2 y with initial UTI should have an US and either a VCUG or nuclear scan performed to detect the presence and severity of VUR
- In the meantime, antibiotic prophylaxis is recommended

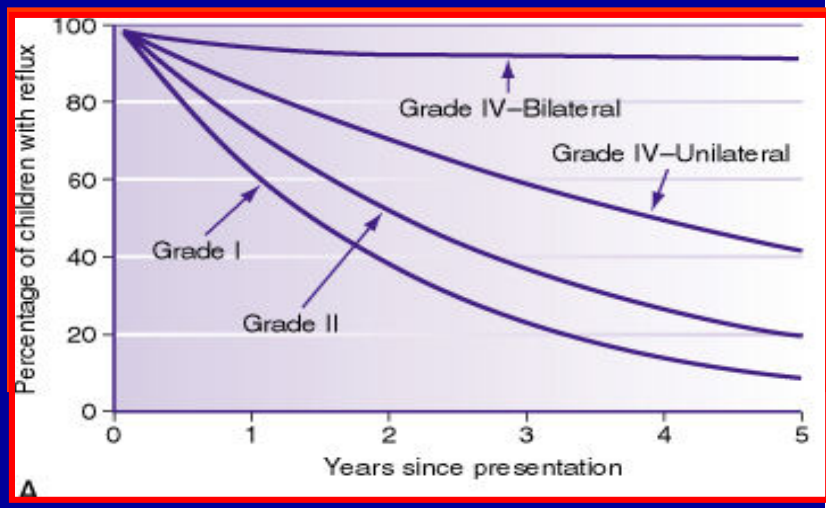
Compliance: imaging 35%, prophylaxis 51%

(Pediatrics 2007)

Vesico-ureteral reflux



- Retrograde passage of urine to the upper urinary tract during urination
- Most common urologic anomaly in children
  - 1% of newborns
  - 35-45% of children with UTI
- Usually resolves spontaneously, depending on grade and bilaterality



Significance of VUR

Garin et al, Pediatrics 2006; 117:626-32

Examined the correlation with renal scarring or recurrent UTI (rUTI) in a randomized study

- 236 3m-18y children with APN
- Grade 1-3 VUR with no other anomalies
- Evaluation:
  - Study entry: US, DMSA renal scan, VCUG
  - 6m: renal scan
  - 12 m: US, VCUG

Significance of VUR

Garin et al, Pediatrics 2006; 117:626-32

Results

- Renal scars: NO VUR: 5.7%
  VUR: 6.2%
  Grade 3: 13.5%

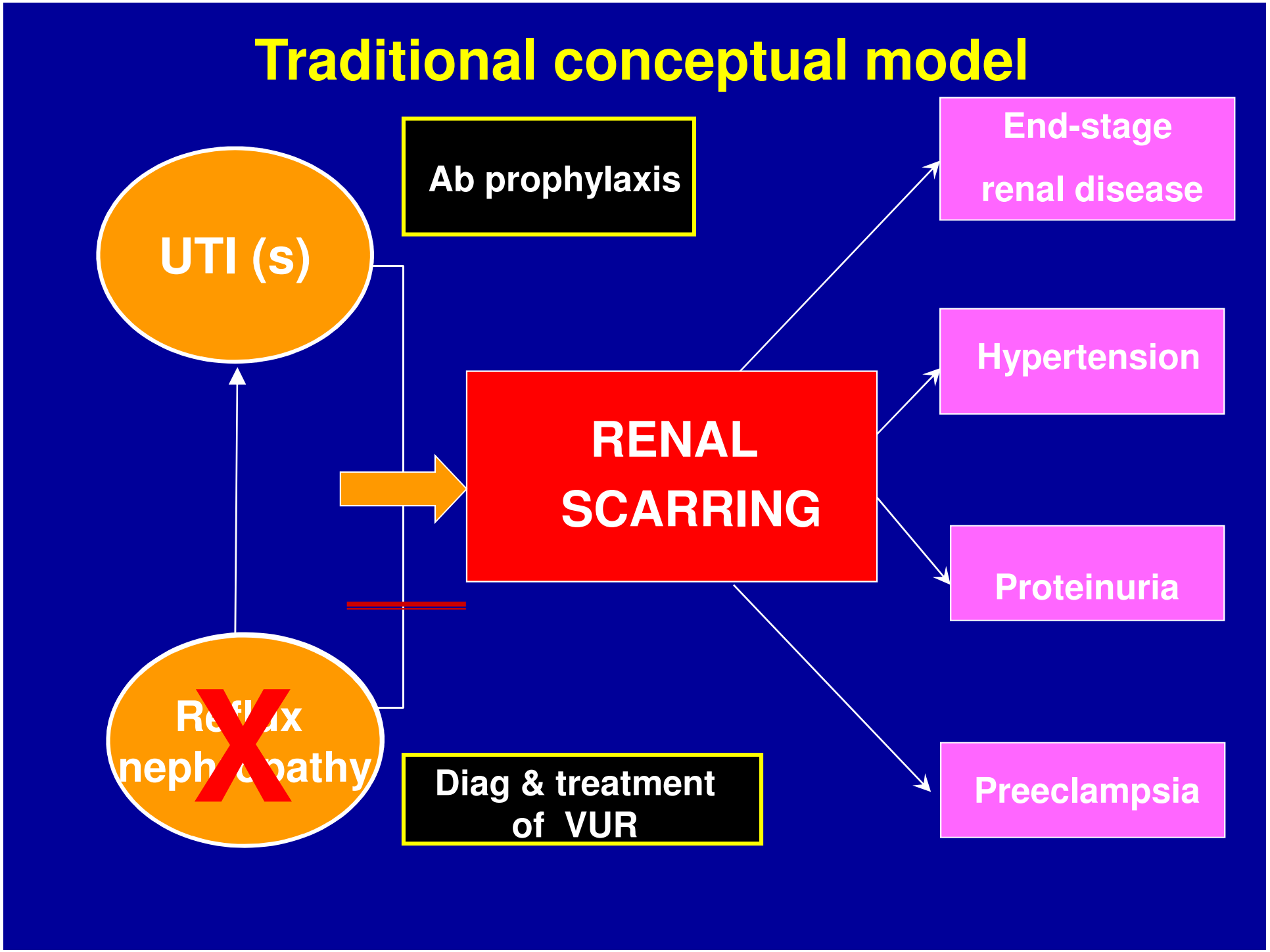
Conclusion

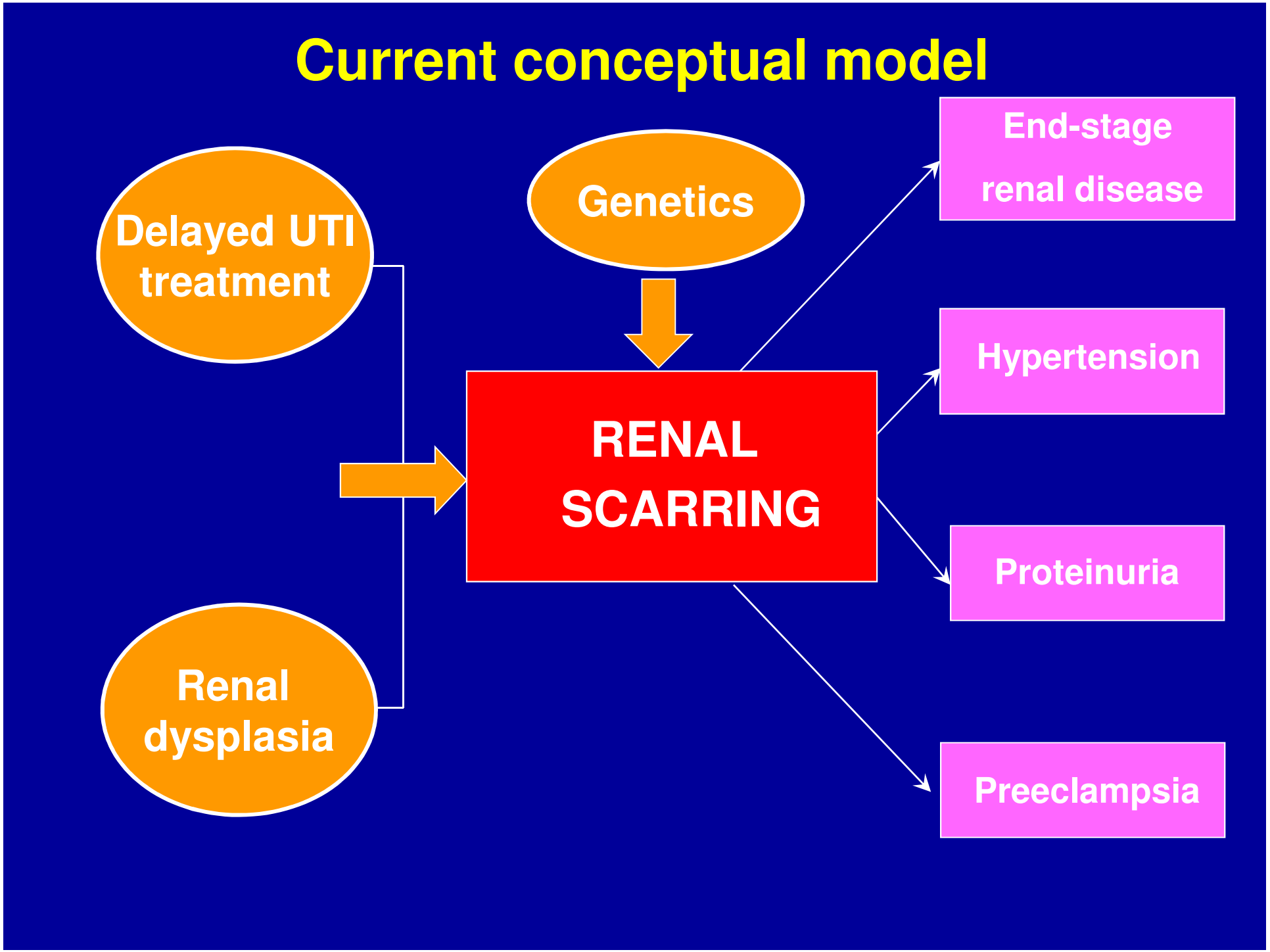
- Low-grade VUR doesn't increase the incidence of renal scarring or of rUTI after APN

Significance of VUR

NEJM 2011;365;239-50

- The Prospective International Reflux Study in Children showed low rates (1%, 1.6%) of long-term complications (10y f/u)
- Renal damage in children with VUR shown in retrospective studies may be related to unrecognized (untreated) UTIs
- Renal scarring is not caused by sterile reflux
- VUR can accompany renal dysplasia, but the causality between VUR and renal damage is currently unclear
- The implications of detecting low-grade reflux is unclear
- Does every child with UTI actually need VCUG???


Traditional conceptual model
Ab prophylaxis
UTI (s)
End-stage
renal disease
Hypertension
RENAL
SCARRING
Proteinuria
Reflux
nephropathy
Diag & treatment
of VUR
Preeclampsia


Current conceptual model
Delayed UTI treatment
Genetics
Renal dysplasia
RENAL SCARRING
End-stage renal disease
Hypertension
Proteinuria
Preeclampsia

American Academy of Pediatrics

FROM THE AMERICAN ACADEMY OF PEDIATRICS

Pediatrics 9/2011;128:595-610

For children 2-24m

- "Febrile infants with UTIs should undergo renal and bladder US"
- Timing: within 2d if infection severe or no clinical response
- Not mandatory if 3rd trimester detailed US available
- VCUG recommended in "atypical or complex" UTI, abnormal US or recurrent febrile UTI
- No recommendation on renal scan, which "rarely affect acute renal management"

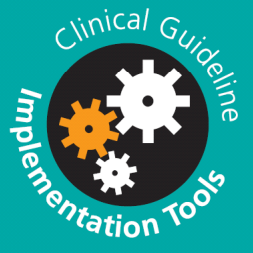
<2m? >2y?

NHS
National Institute for
Health and Clinical Excellence

Urinary tract infection in children

Implementing NICE guidance

NICE clinical guideline 54



GUIDELINES

Diagnosis and management of urinary tract infection in children: summary of NICE guidance

Rintaro Mori,[1] Monica Lakhanpaul,[2] Kate Verrier-Jones[3] on behalf of the Guideline Development Group

Box 3 | Main characteristics of patients with atypical or recurrent urinary tract infection

Atypical (any of the following)

- Septicaemia or patient who looks seriously ill (see NICE guideline[2])
- Poor urine flow
- Abdominal or bladder mass
- Raised creatinine concentration
- Failure to respond to treatment with suitable antibiotics within 48 hours
- Infection with non-Escherichia coli organisms

Recurrent (any of the following)

- Two or more episodes of urinary tract infection with acute pyelonephritis or upper urinary tract infection
- One episode of urinary tract infection with acute pyelonephritis or upper urinary tract infection plus one or more episode of urinary tract infection with cystitis or lower urinary tract infection
- Three or more episodes of urinary tract infection with cystitis or lower urinary tract infection

Urinary anomalies according to pathogen

PIDJ 2005;24:581-5, Infection 2008;36:421-6

Pathogen	Urinary abnormalities	p value
E. coli	41.2%	-
Non *E. coli*	65.7%	P<0.001
Enterococcus sp	70.1%	P=0.03
P. aeruginosa	100%	P<0.001

Imaging in infants <6m

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes	Yes
Ultrasound within 6 weeks	Yes	No	No
DMSA 4–6 mo following the acute infection	No	Yes	Yes

Imaging in children 6m-3y

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	No	No

Imaging in children ≥3y

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4–6 months following the acute infection	No	No	Yes
MCUG	No	No	No

Imaging in a child with UTI

"Top-Down approach" – 5-y prospective study

J Urol 10/2010;184:1708-10

- **Rationale:** VCUG focuses on diagnosing VUR,
  DMSA scan focuses on the target – renal damage
- **Criticism:** This approach can miss some VUR and preventable renal damage
- **Methods:** US, scan, VCUR after UTI with 5y F/U
- **Results:** No child with a normal initial scan had significant VUR; abnormal F/U scan was not related to VUR
- **Conclusion:** "DMSA scan can predict clinically sig reflux and children at greatest risk"

Imaging in a child with UTI

- **<6m**

  Smooth course: US within 6w (detect anomalies, renal size and parenchyma)

  Atypical UTI: US within 2d; scan 6m after UTI

- **6m-3y**

  Smooth course: US (<2y?)

  Atypical UTI: US within 2d; scan 6m after UTI

- **≥3y**

  Smooth course: No imaging

  Atypical UTI: US only

  Recurrent UTI: US and renal scan

- **VCUG – not recommended routinely; individualized according to course and findings on US or scan**
- **CT or MRI – rarely; on individual basis**

Address http://content.nejm.org/cgi/content/short/361/18/1748

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ORIGINAL ARTICLE

◂ Previous Volume 361:1748-1759 October 29, 2009 Number 18 Next ▸

Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

Jonathan C. Craig, M.B., Ch.B., Ph.D., Judy M. Simpson, Ph.D., Gabrielle J. Williams, Ph.D., M.P.H., Alison B.Sc., Graham J. Reynolds, M.B., B.S., Steven J. McTaggart, M.B., B.S., Ph.D., Elisabeth M. Hodson, M.B., Jonathan R. Carapetis, M.B., B.S., Ph.D., Noel E. Cranswick, M.B., B.S., Grahame Smith, M.B., B.S., Les M. M.B., B.Ch., Ph.D., Patrina H.Y. Caldwell, Ph.D., Sana Hamilton, M.P.H., Leslie P. Roy, M.B., B.S., for the Pre of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIV Investigators

Internet

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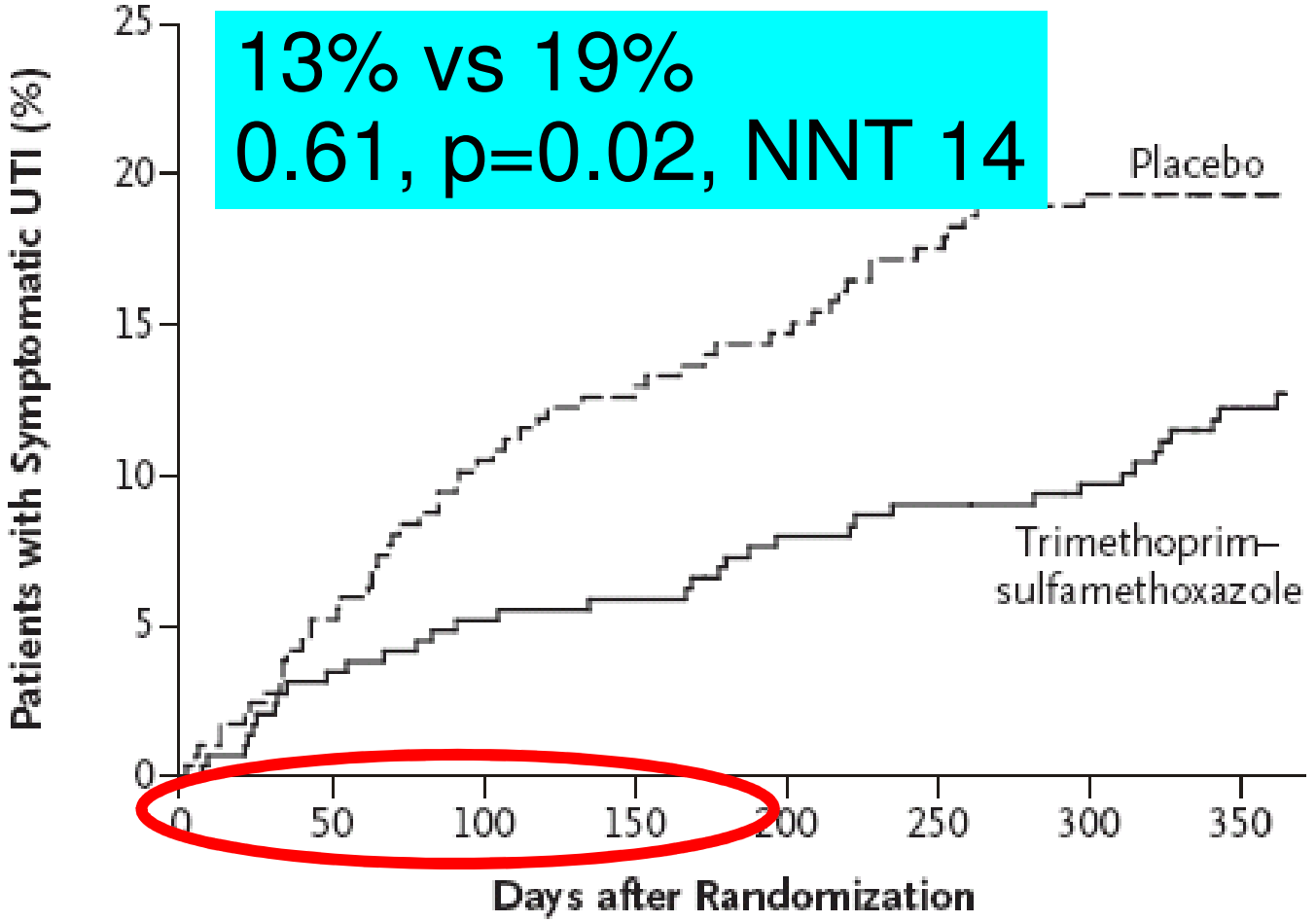
The NEW ENGLAND JOURNAL of MEDICINE

Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

- Children with symptomatic culture + UTI, with or without VUR enrolled over 10 years
- After initial treatment, randomly assigned to low-dose TMP/SMX prophylaxis or placebo for 12m
- Imaging not mandatory
- Compliance assessed every 3m during visits
- Followed for symptomatic UTI and other variables
- 9482 children with UTI reviewed, 2960 eligible, 576 enrolled, 12 lost of follow-up

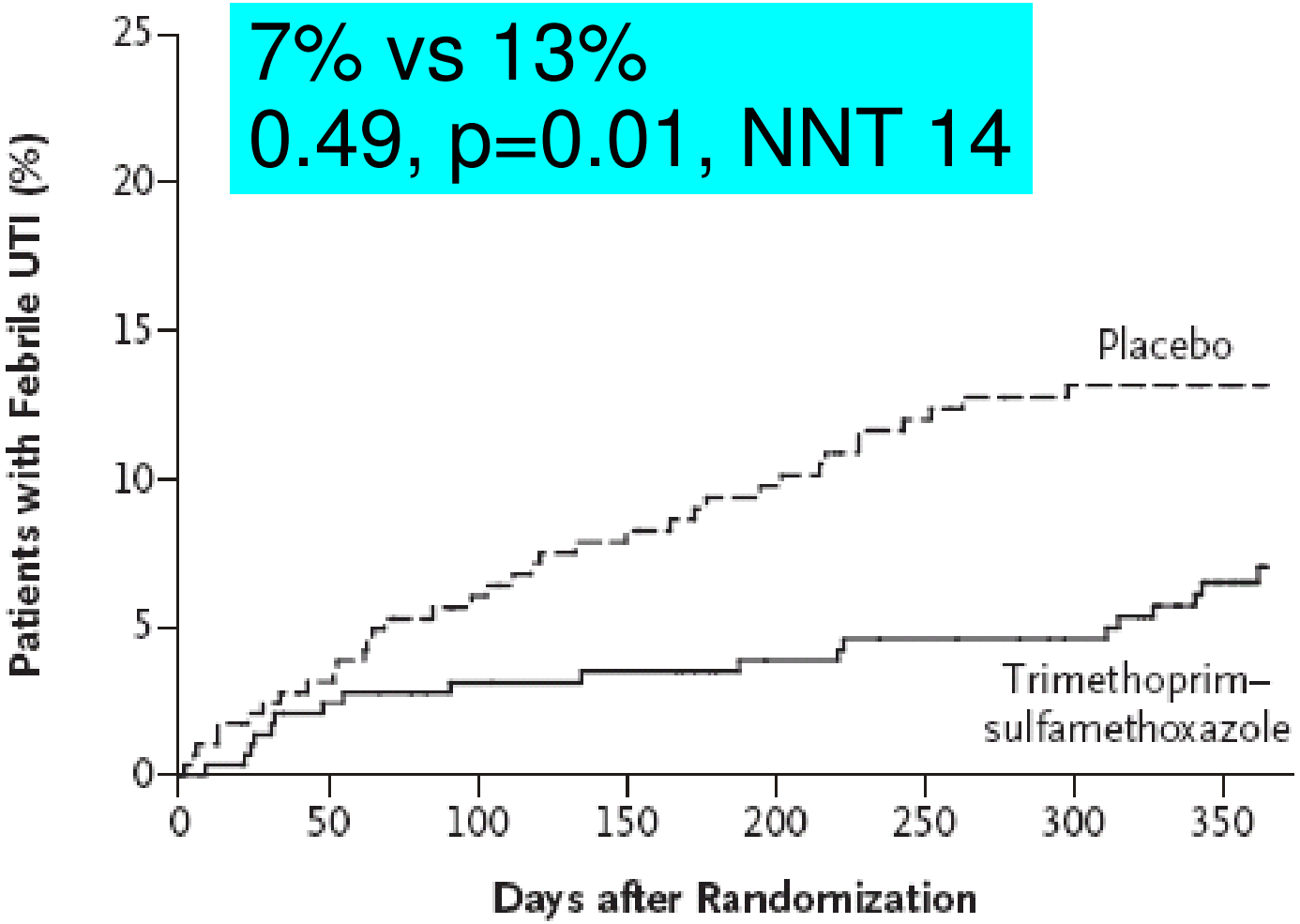
13% vs 19%
0.61, p=0.02, NNT 14



No. at Risk								
Antibiotic	288	278	273	271	264	261	257	216
Placebo	288	271	254	248	242	232	225	208

Figure 2. Time to Symptomatic Urinary Tract Infection (UTI) (Primary Outcome).

7% vs 13%
0.49, p=0.01, NNT 14



No. at Risk								
Antibiotic	288	278	273	271	264	261	257	216
Placebo	288	271	254	248	242	232	225	208

Figure 4. Time to Urinary Tract Infection (UTI) with Fever (Secondary

Results

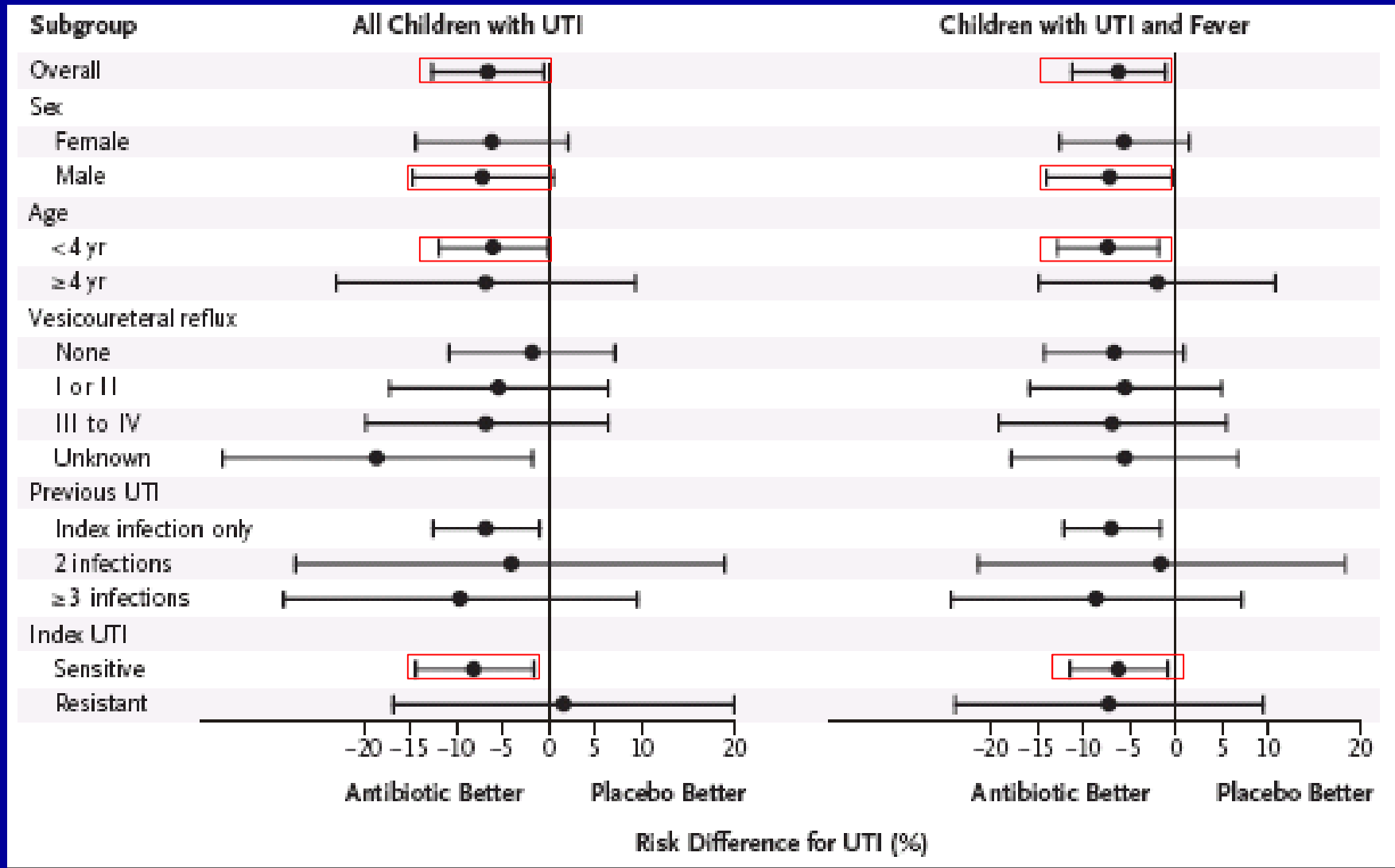
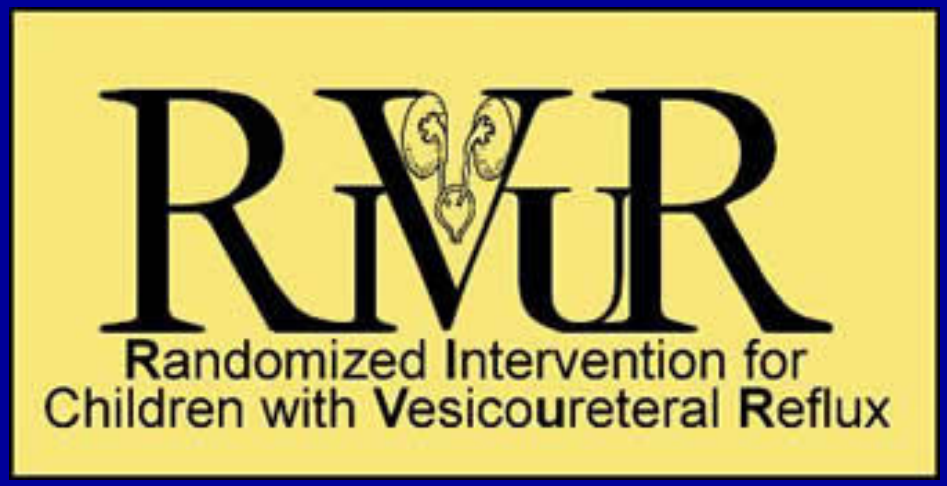


Figure 3. Effect of Trimethoprim–Sulfamethoxazole on the Risk of Symptomatic Urinary Tract Infection (UTI) with and without Fever.

Table 2. Secondary Outcomes.

Outcome	Antibiotic Group (N = 288)	Placebo Group (N = 288)	Risk Difference (95% CI)*	P Value
	no. (%)			
Urinary tract infection with fever†	19 (7)	36 (13)	6 (1 to 11)	0.01
Hospitalization for urinary tract infection	23 (8)	29 (10)	2 (−3 to 7)	0.38
Urinary tract infection with organism resistant to trimethoprim–sulfamethoxazole‡	24 (67)	13 (25)	−42 (−61 to −22)	<0.001
Adverse drug reaction	4 (1)	10 (3)	2 (0 to 5)	0.10
Use of antibiotic for other infectious disease				
Any episode	123 (43)	141 (49)	6 (−2 to 14)	0.13
No. of episodes				
0	165 (57)	147 (51)		0.04§
1	66 (23)	65 (23)		
2	37 (13)	42 (15)		
3	12 (4)	18 (6)		
4	3 (1)	11 (4)		
≥5	5 (2)	5 (2)		
Renal scan at 1 yr¶				
No. of patients	71	83		
Normal results at baseline	36 (51)	45 (54)	4 (−12 to 19)	0.87
Unchanged	12 (17)	28 (34)		



- Multicenter randomized placebo-controlled study
- 15 US centers, 600 children
- Initial UTI, presence of grades I-IV VUR
- TMP/SMX prophylaxis vs placebo
- 2y follow-up

Regarding rapid progress -as has been estimated

In 7 years
half of what I told
today
will be wrong

Unfortunately
I can not tell you
which half...