

# Urinary Tract Infections

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# Disclosures

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None

# Outline

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## **Introduction:**

Epidemiology, Gaps in the clinical care of rUTI, Causes of rUTI

## **Pathogenesis:**

Host susceptibility factors, Microbial Factors

## **Treatment:**

Current common practices to prevent rUTI and their pros and cons

## **On-going studies:**

Update on newer anti-infective strategies



# Introduction

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Urinary Tract Infections (UTIs) are one of the most common infections in children 1.

Of the estimated annual national \$2.5 billion cost for UTI management in the US, the aggregate hospital costs of pediatric UTI management exceeds \$520 million.

Antibiotics are prescribed in about 70% of all pediatric clinic visits for UTIs, with a significant rise in the prescription of broad third generation cephalosporins (12% in 1998-2000 vs. 25% in 2005-2007).

# Prevalence

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The pooled prevalence of UTI among febrile females:

<3 months- 7.5%

3-6 months-5.7%

6-12 months- 8.3%

>12 months-2.1%

Overall, the pooled prevalence of UTIs in children and adolescents <19 yrs of age is 7.8%, including both febrile and afebrile episodes.

A retrospective review of almost 75,000 pediatric patients <6 yrs of age determined the rate of recurrent UTI (rUTI) to be 13.6%, i.e. an incidence rate of 0.12 per person-year, among otherwise healthy children.

# Risk of UTI

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

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
$\leq 1\%$	No more than 1
$\leq 2\%$	No more than 2

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

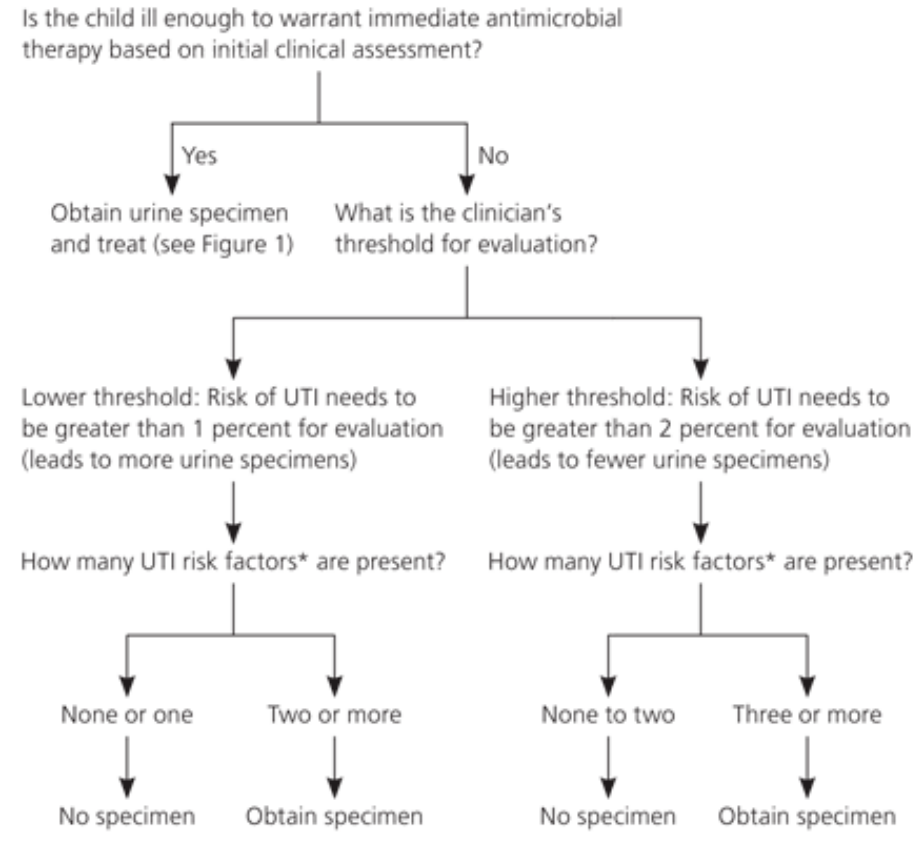
Recurrent UTI is defined as the onset of symptoms after the resolution of a previous urinary tract infection. According to American Association of Pediatricians (AAP) guidelines, three or more episodes of UTIs in a period of 12 months signify recurrence .

**FIGURE 2**

Probability of UTI Among Febrile Infant Girls<sup>28</sup> and Infant Boys<sup>30</sup> According to Number of Findings Present. <sup>a</sup>Probability of UTI exceeds 1% even with no risk factors other than being uncircumcised.

# Diagnosis

## Guideline for Obtaining Urine Specimens in Febrile Girls



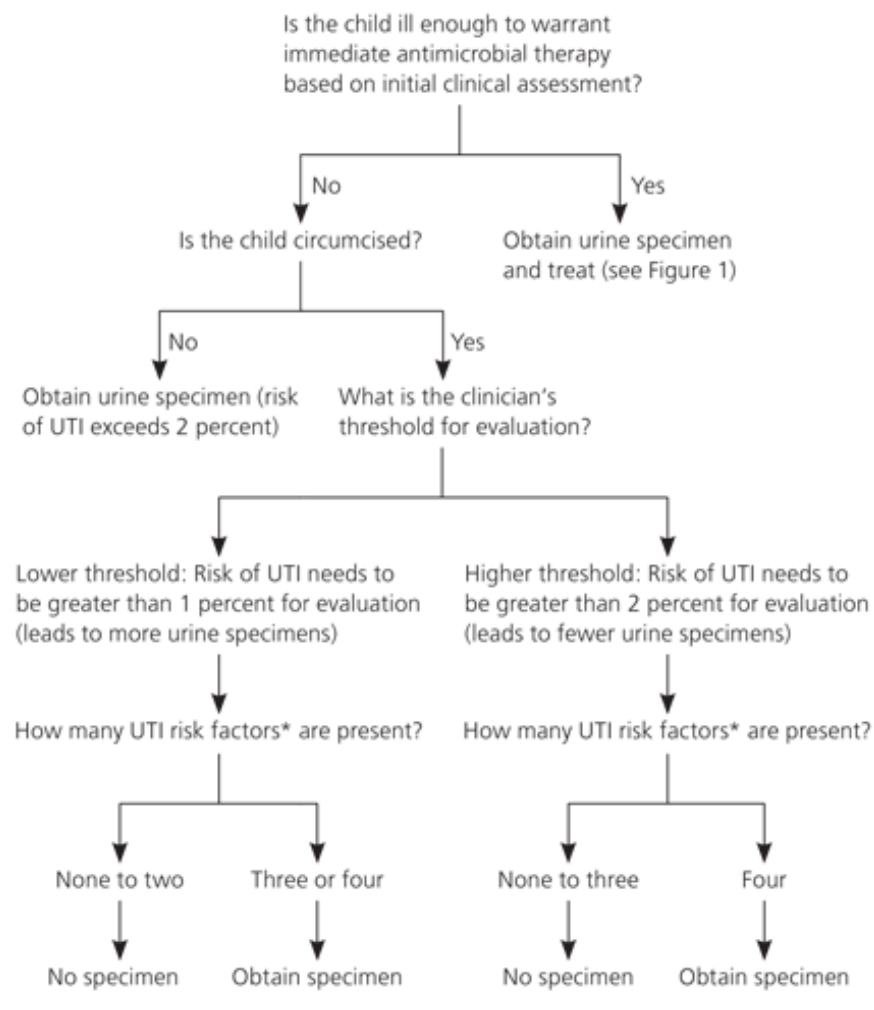
\*—Risk factors: white race, age younger than 12 months, temperature of at least 102.2°F (39°C), fever lasting at least two days, absence of another source of infection.

Figure 2.

Algorithm for deciding when to obtain a urine specimen in girls two to 24 months of age with unexplained fever; based on the clinician's threshold for risk. (UTI = urinary tract infection.)

Information from reference 4.

## Guideline for Obtaining Urine Specimens in Febrile Boys



\*—Risk factors: nonblack race, temperature of at least 102.2°F (39°C), fever lasting more than 24 hours, absence of another source of infection.

Figure 3.

Algorithm for deciding when to obtain a urine specimen in boys two to 24 months of age with unexplained fever; based on the clinician's threshold for risk. (UTI = urinary tract infection.)

Information from reference 4.



# Diagnostic tests

**TABLE 1** Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

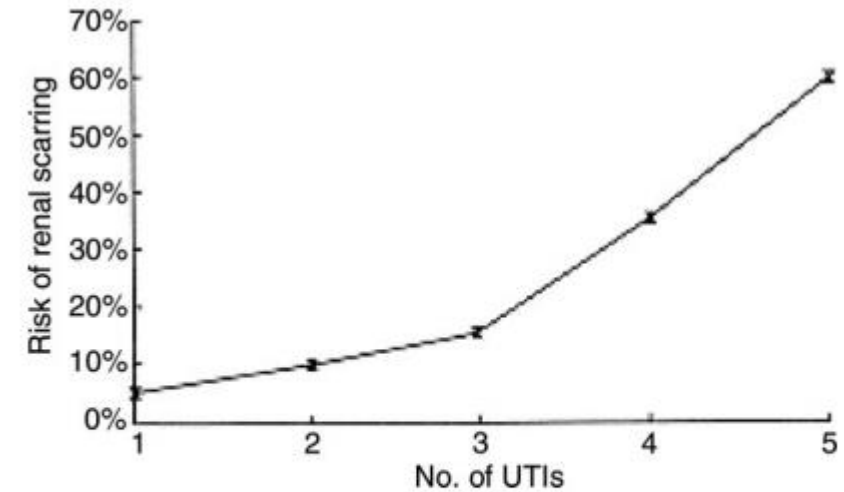
Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67–94)	78 (64–92)
Nitrite test	53 (15–82)	98 (90–100)
Leukocyte esterase or nitrite test positive	93 (90–100)	72 (58–91)
Microscopy, WBCs	73 (32–100)	81 (45–98)
Microscopy, bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase test, nitrite test, or microscopy positive	99.8 (99–100)	70 (60–92)

- The conversion of dietary nitrates to nitrites by uropathogens in the bladder takes approximately 4 hrs. Therefore the traditional nitrite test is not sensitive in children, particularly in infants, who frequently empty their bladders
- The standard method of assessing urine for pyuria has been microscopic analysis of centrifuged urine with a threshold of 5 WBCs per high-power field (~25 WBCs per  $\mu\text{l}$ ).
- When a counting chamber is used, a finding of at least 10 WBCs per  $\mu\text{l}$  of uncentrifuged urine is considered a sensitive indicator of UTIs especially among infants.
- A urine culture result of  $\geq 50,000$  CFUs per mL of a single urinary pathogen is considered diagnostic for UTI.

# Renal scarring

**TABLE 5** Rates of VUR According to Grade in Hypothetical Cohort of Infants After First UTI and After Recurrence

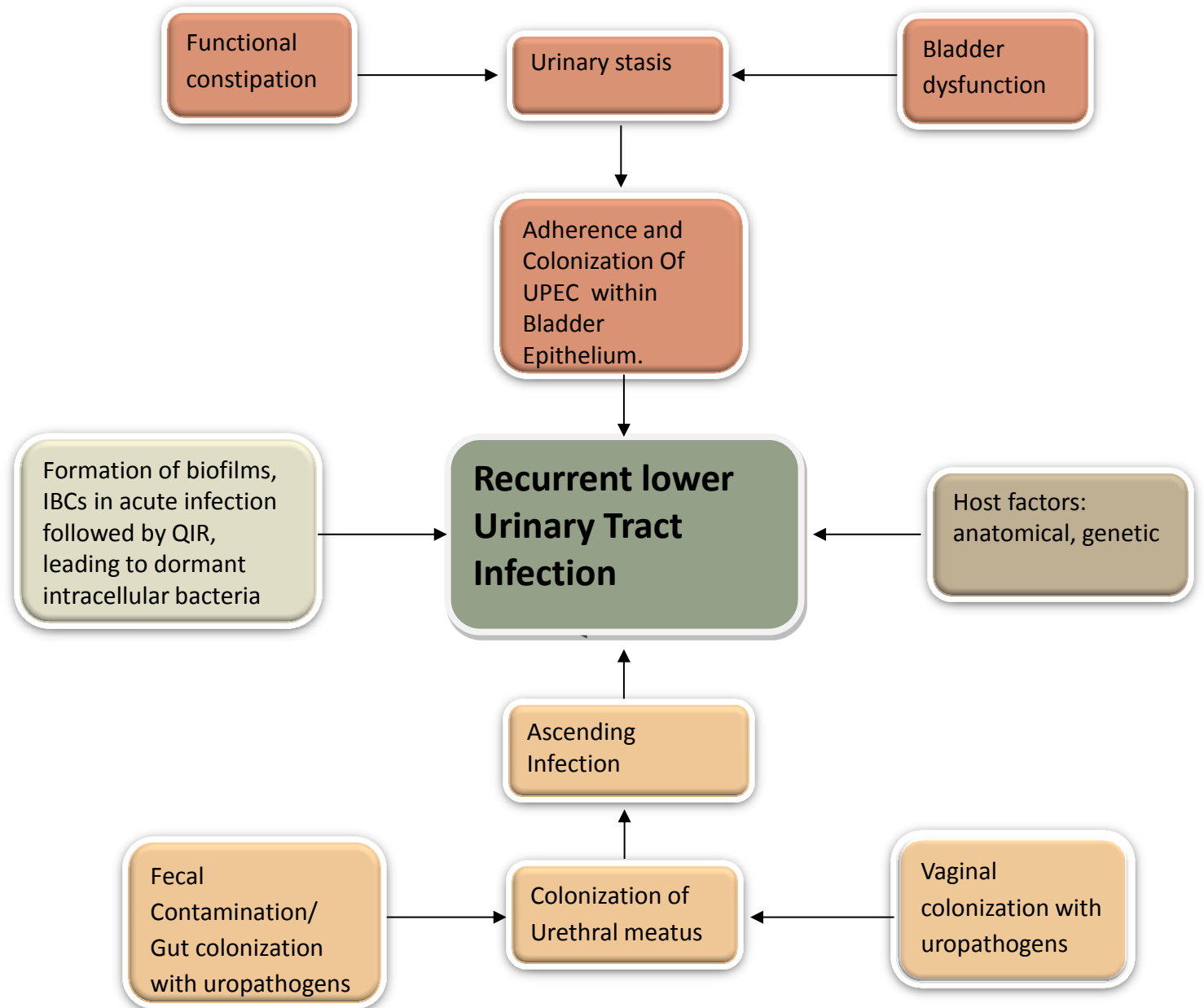
	Rate, %	
	After First UTI ( <i>N</i> = 100)	After Recurrence ( <i>N</i> = 10)
No VUR	65	26
Grades I–III VUR	29	56
Grade IV VUR	5	12
Grade V VUR	1	6



**FIGURE 4**

Relationship between renal scarring and number of bouts of pyelonephritis. Adapted from Jodal.<sup>59</sup>

# Overview of pathogenesis of rUTI



# Urinary stasis

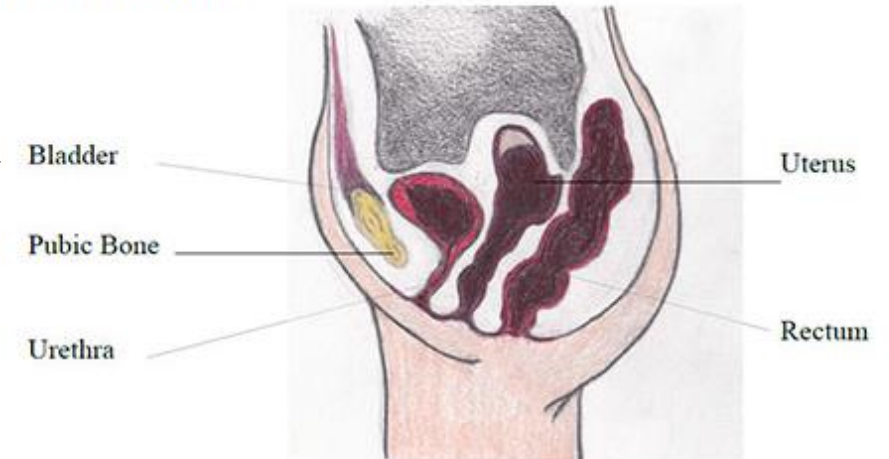
Up to one-third of girls with constipation also have rUTIs.

Functional constipation causes urinary stasis due to compression of the bladder and elongation of the urethra by fecal retention and expansion of the sigmoid colon and rectum, which in turn reduces urinary flow and promotes urinary pathogen adherence.

Children with functional constipation are also found to have renal pelvic dilation even in the absence of anatomical abnormalities or infection.

Voiding dysfunction, including urinary incontinence and post-void residual urine, results in a higher rate of rUTI especially in girls.

Normal Bowel



Constipated Bowel



<https://www.cincinnatichildrens.org/health/c/constipation-dysfunction>

# Vesicoureteral reflux

A retrospective study with more than 600 children with UTI showed that grade IV and V vesicoureteral reflux (VUR), is associated with an increased risk of rUTI, however, grades I-III are not.

**Table 1.** First and Recurrent Urinary Tract Infection (UTI) in The Children's Hospital of Pennsylvania Primary Care Cohort

Characteristic	No. (%)	
	First UTI (n = 611)	Recurrent UTI (n = 83)
Sex		
Male <sup>a</sup>	68 (11.1)	8 (9.6)
Female	543 (88.9)	75 (90.4)
Race		
White	343 (56.1)	54 (65.1)
Nonwhite	268 (43.9)	29 (34.9)
Age, y		
<2	236 (38.6)	26 (31.3)
2-6	375 (61.4)	57 (68.7)
VCUG result		
Not performed	400 (65.5)	52 (62.7)
Normal	154 (25.2)	20 (24.1)
VUR grade 1-3	50 (8.2)	8 (9.6)
VUR grade 4-5	7 (1.1)	3 (3.6)
Any exposure to antimicrobial prophylaxis		
No	483 (79.1)	64 (77.1)
Yes	128 (20.9)	19 (22.9)

Abbreviations: VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

<sup>a</sup>Among male children, there was no documented circumcision status for 32 (47%); of those with documented status, 26 (38%) were uncircumcised, and 10 (15%) were circumcised.

**TABLE 2** Clinical Outcomes According to VUR Status

Outcome	VUR Status, n (%)				Unadjusted Comparison of VUR Versus No VUR Group	Adjusted Comparison of VUR Versus No VUR Group <sup>a</sup>
	No VUR	VUR	Grade I-II	Grade III-IV		
Recurrent <i>r/s</i> UTI <sup>b</sup>	(n = 195)	(n = 305)	(n = 167)	(n = 138)	1.52 (1.01–2.29)	HR (95% CI) 1.58 (1.04–2.42)
	33 (17.3)	72 (25.4)	35 (22.4)	37 (28.9)		
Renal scarring <sup>c</sup>	(n = 144)	(n = 235)	(n = 126)	(n = 109)	1.93 (0.84–4.43)	OR (95% CI) 2.05 (0.86–4.87)
Overall <sup>d</sup>	8 (5.6)	24 (10.2)	9 (7.1)	15 (13.8)		
Mild	7 (4.9)	13 (5.5)	5 (4.0)	8 (7.3)		
Moderate	1 (0.7)	5 (2.1)	1 (0.8)	4 (3.7)		
Severe	0 (0)	4 (1.7)	3 (2.4)	1 (0.9)		
Global atrophy	0 (0)	2 (0.9)	0 (0)	2 (1.8)		
New <sup>e</sup>	6 (4.3)	19 (8.4)	8 (6.5)	11 (10.6)	2.06 (0.80–5.28)	2.05 (0.77–5.48)

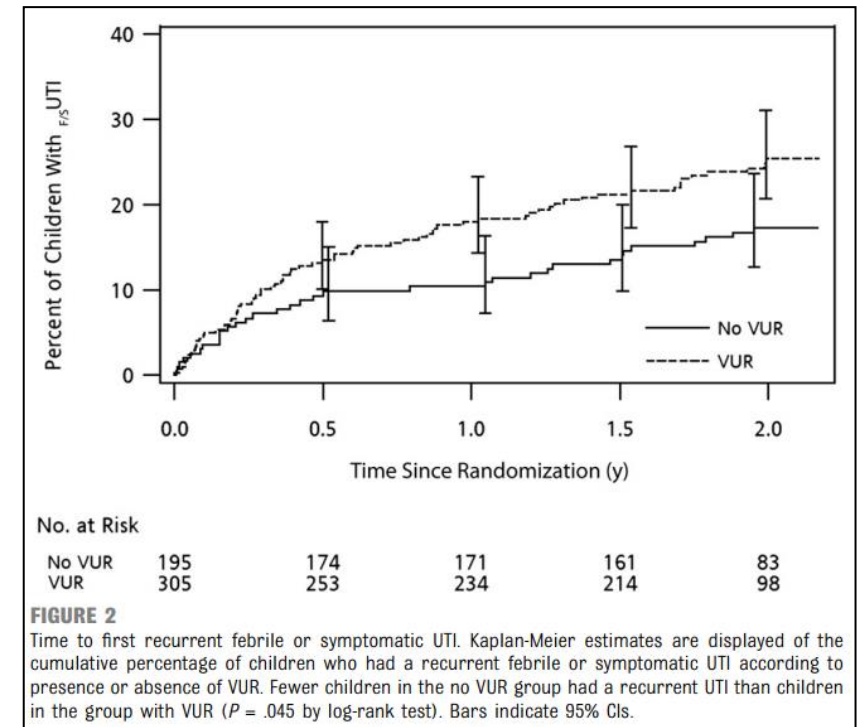
<sup>a</sup> Adjusted for BBD at baseline (absent or present, not toilet-trained), age in months (2–11, 12–23, 24–35, and ≥36), race (white versus non-white), and type of index UTI (febrile versus symptomatic).

<sup>b</sup> Percentages based on Kaplan-Meier 2-year estimates.

<sup>c</sup> Defined as decreased uptake of tracer that was associated with loss of contours or the presence of cortical thinning with decreased volume. Due to the limited number of children with severe scarring, odds ratios were calculated by using Firth's penalized likelihood method.

<sup>d</sup> Refers to scarring present at the end of 2 years, whether it was new or present at study entry.

<sup>e</sup> Defined as scarring on the outcome renal scan with DMSA that was not present at baseline. N's for new scarring were as follows: no VUR, n = 141; VUR, n = 227; grade I and II, n = 123; and grade III and IV, n = 104.



Prospective cohort study on 307 children with VUR and 197 children without VUR over a two year period showed a higher rate of recurrence in children with any grade of VUR compared to those with no VUR.

Among children with any grade of VUR, those that were less than 24 months old or were diagnosed with bowel and bladder dysfunction (BBD) were at a higher risk of rUTI.

# Male circumcision and antibiotic use

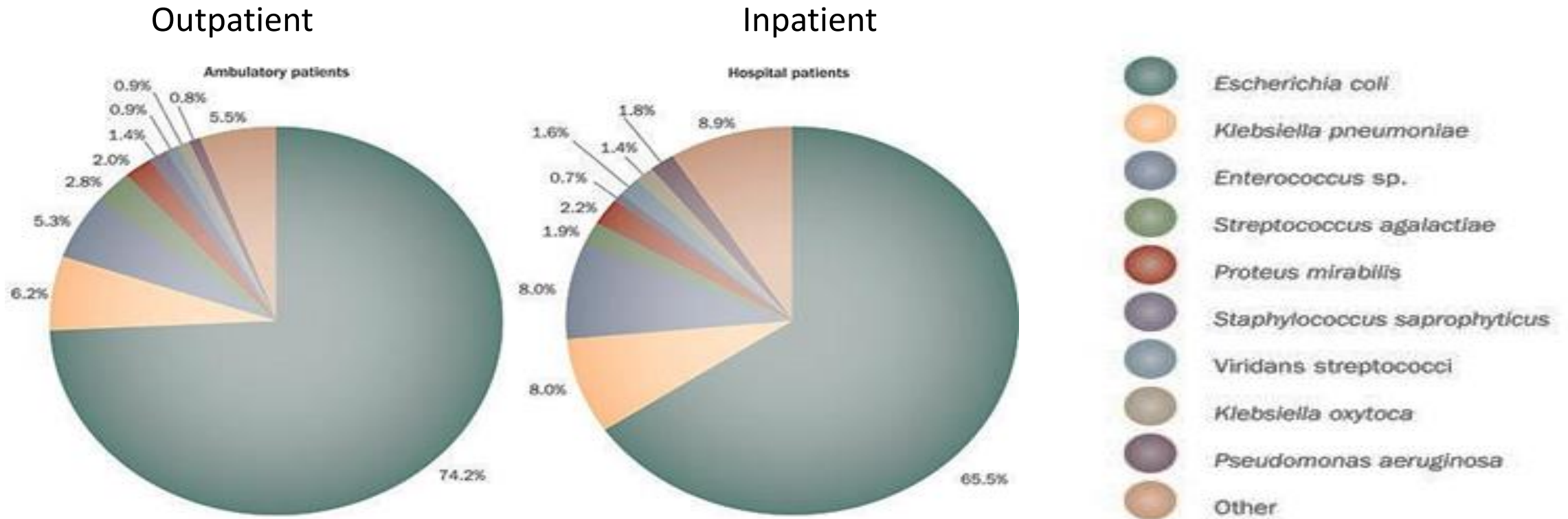
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Among otherwise healthy male neonates, there is a greater than 10 fold increase in the incidence of UTI among children who are uncircumcised.

Normal vaginal colonization with H<sub>2</sub>O<sub>2</sub> producing strains of *Lactobacillus* inhibits colonization with uropathogenic *E. coli* (UPEC). Therefore, use of antibiotics that alter the normal vaginal flora may also increase the risk of rUTI among females.



# Etiology of Urinary Tract Infection (UTI) According to Population





# Host susceptibility factors

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The urinary tract milieu is hostile to bacterial survival due to the existence of several defense mechanisms.

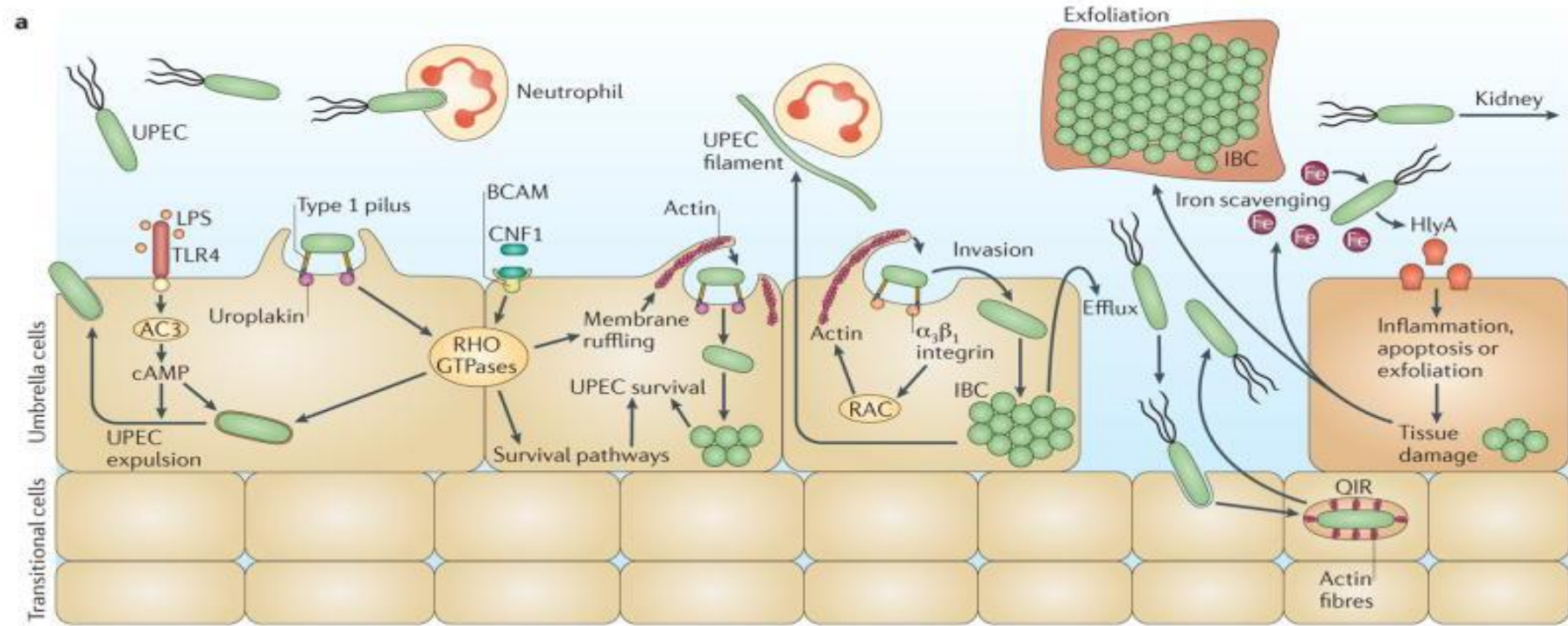
The innate system including mucosal barriers, polymorphonuclear leukocyte infiltration, activation of the complement pathway, and release of antimicrobial peptides.

TLR-4: The foremost innate response to infection with UPEC is through the LPS sensing pattern recognition receptor, Toll-like receptor 4 (TLR4). Children with asymptomatic bacteriuria are more likely to have *tlr4* promoter polymorphisms associated with reduced expression of TLR4. Among women with rUTI, approximately 42% have a family history of cystitis compared to 11% of controls.

CXCR-1: a receptor for the chemokine IL-8 also known as the neutrophil chemotactic factor. Inherited polymorphisms in children result in reduced expression and predisposes them to acute pyelonephritis.

Neutrophil gelatinase-associated lipocalin (NGAL): It is known to be upregulated during UTI and has a bacteriostatic effect possibly through iron chelation. Children with rUTI appear to have significantly lower levels of urinary NGAL compared to controls.

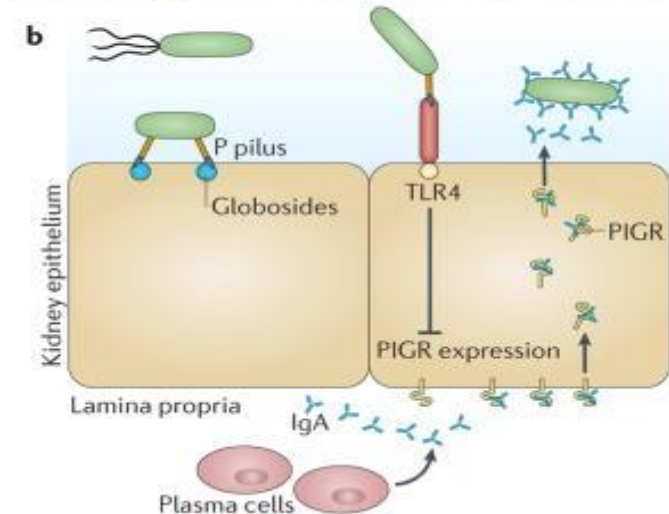
# Microbial factors



UPEC: Uropathogenic *E. coli*

IBC: Intracellular bacterial colonies

QIR: Quiescent intracellular bacteria



# Current practices to prevent UTI

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# Prophylactic antibiotics

**TABLE 4** Recurrences of Febrile UTI/Pyelonephritis in Infants 2 to 24 Months of Age With and Without Antimicrobial Prophylaxis, According to Grade of VUR

Reflux Grade	Prophylaxis		No Prophylaxis		<i>P</i>
	No. of Recurrences	Total <i>N</i>	No. of Recurrences	Total <i>N</i>	
None	7	210	11	163	.15
I	2	37	2	35	1.00
II	11	133	10	124	.95
III	31	140	40	145	.29
IV	16	55	21	49	.14

# RIVUR Trial

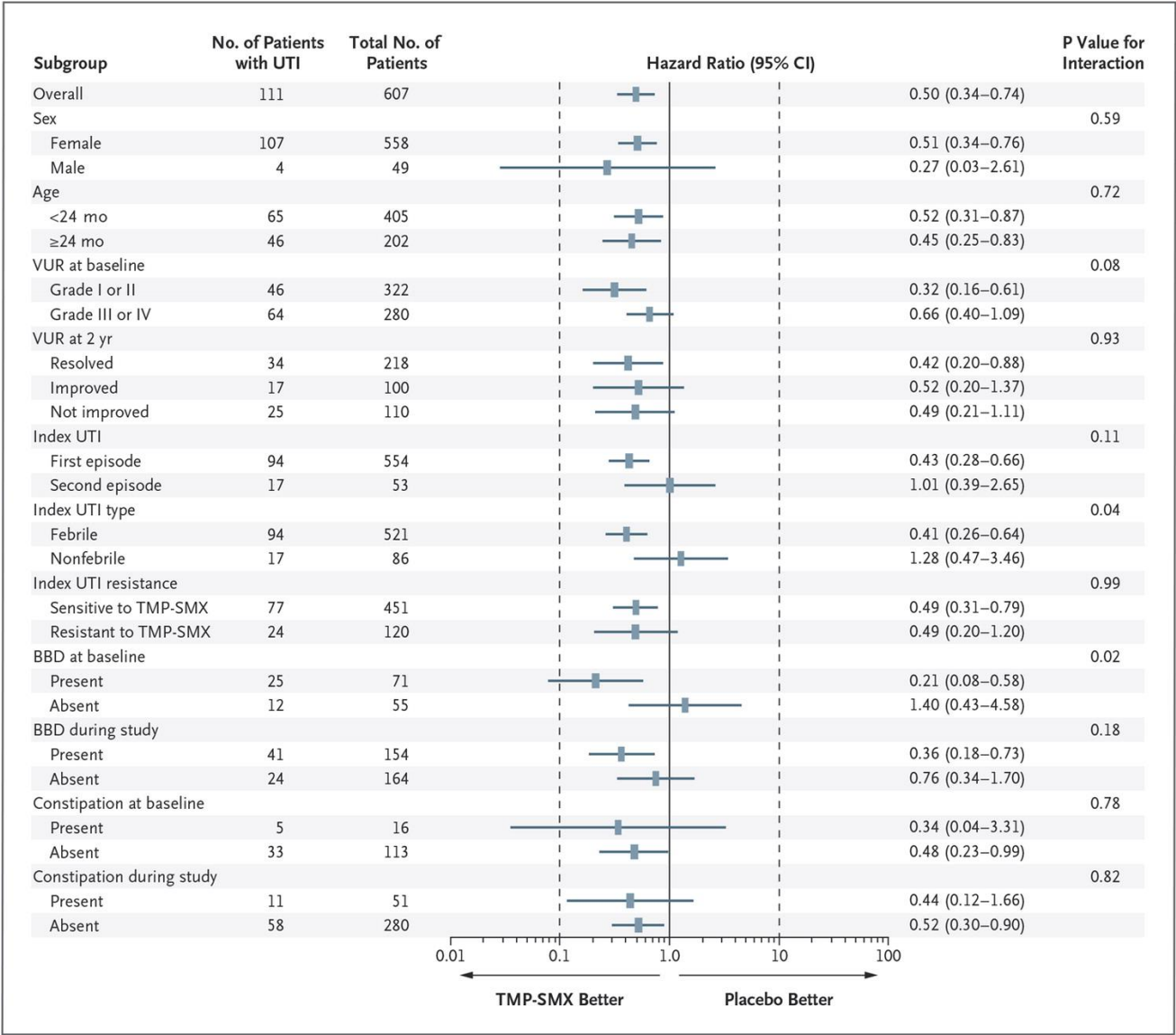
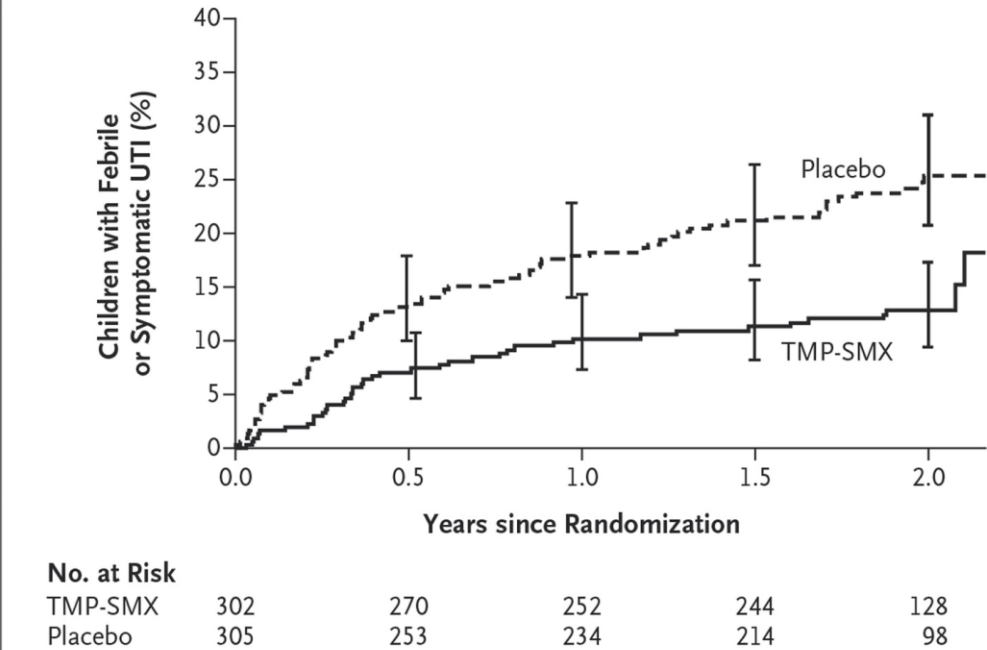
The RIVUR clinical trial randomized more than 600 children to receive either trimethoprim–sulfamethoxazole (TMP-SMX) or placebo for 2 years, showed an approximate 50% reduction in rUTI, irrespective of the severity of VUR, with a Number Needed to Treat (NNT) of 8.

However, 63% of the recurrences in the prophylaxis group were due to TMP-SMX resistant *E. coli*, which is concerning given the rapid rise in antimicrobial resistance in the recent years.

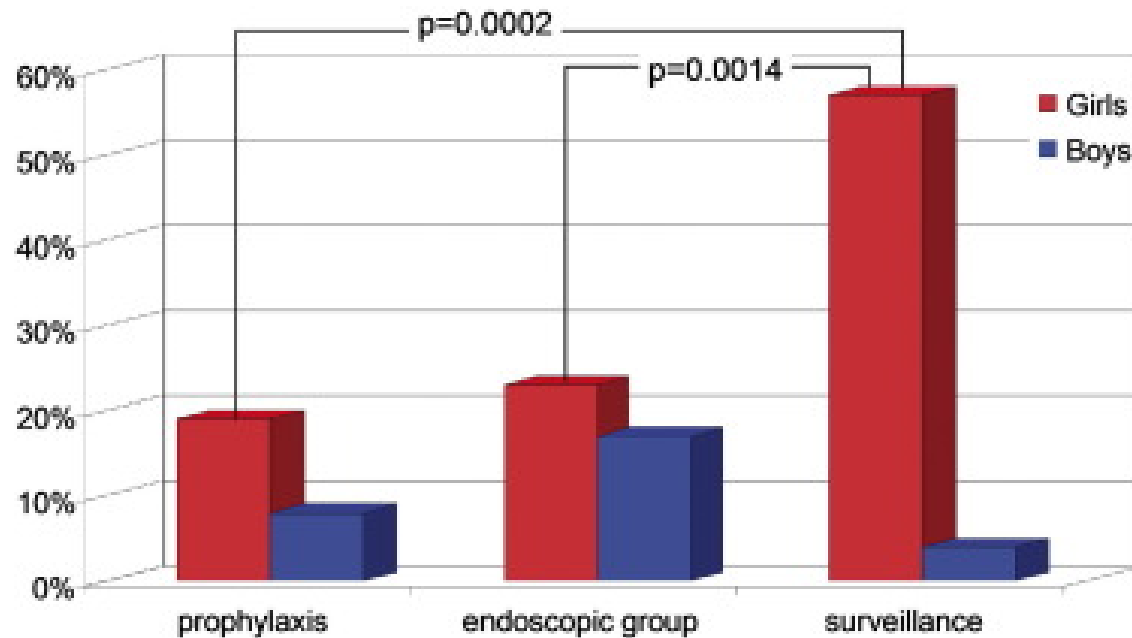
Furthermore, prophylaxis did not reduce the incidence of renal scarring, which precedes end stage renal disease and is the primary justification for prophylaxis

**Table 2. Clinical Outcomes According to Study Group.**

Outcome	Trimethoprim– Sulfamethoxazole <i>no. of children/total no. (%)</i>	Placebo	Absolute Difference in Risk (95% CI) <i>percentage points</i>
Recurrent febrile or symptomatic UTI*			
Children with missing 2-yr data classified as having had an event (intention-to-treat analysis)	77/302 (25.5)	114/305 (37.4)†	11.9 (4.6 to 19.2)
Children with missing 2-yr data classified as not having had an event (intention-to-treat analysis)‡	39/302 (12.8)	72/305 (25.4)§	12.6 (6.1 to 19.0)
Children with missing 2-yr data omitted	39/264 (14.8)	72/263 (27.4)§	12.6 (5.7 to 19.5)
Treatment failure‡¶	14/302 (5.0)	27/305 (9.6)	4.5 (0.2 to 8.8)
Renal scarring**			
Overall	27/227 (11.9)	24/235 (10.2)	–1.7 (–7.4 to 4.0)
Severe††	9/227 (4.0)	6/235 (2.6)	–1.4 (–4.7 to 1.8)
New‡‡	18/220 (8.2)	19/227 (8.4)	0.2 (–4.9 to 5.3)
Any cortical defect	29/227 (12.8)	25/235 (10.6)	–2.1 (–8.0 to 3.7)
Antimicrobial resistance			
Resistant <i>Escherichia coli</i> in stool	56/203 (27.6)	41/210 (19.5)	–8.1 (–16.2 to 0.1)
First recurrent febrile or symptomatic UTI with resistant <i>E. coli</i>	19/30 (63.3)§§	11/57 (19.3)	–44.0 (–64.1 to –24.0)
First recurrent febrile or symptomatic UTI with any resistant pathogen	26/38 (68.4)§§	17/69 (24.6)	–43.8 (–61.7 to –25.8)



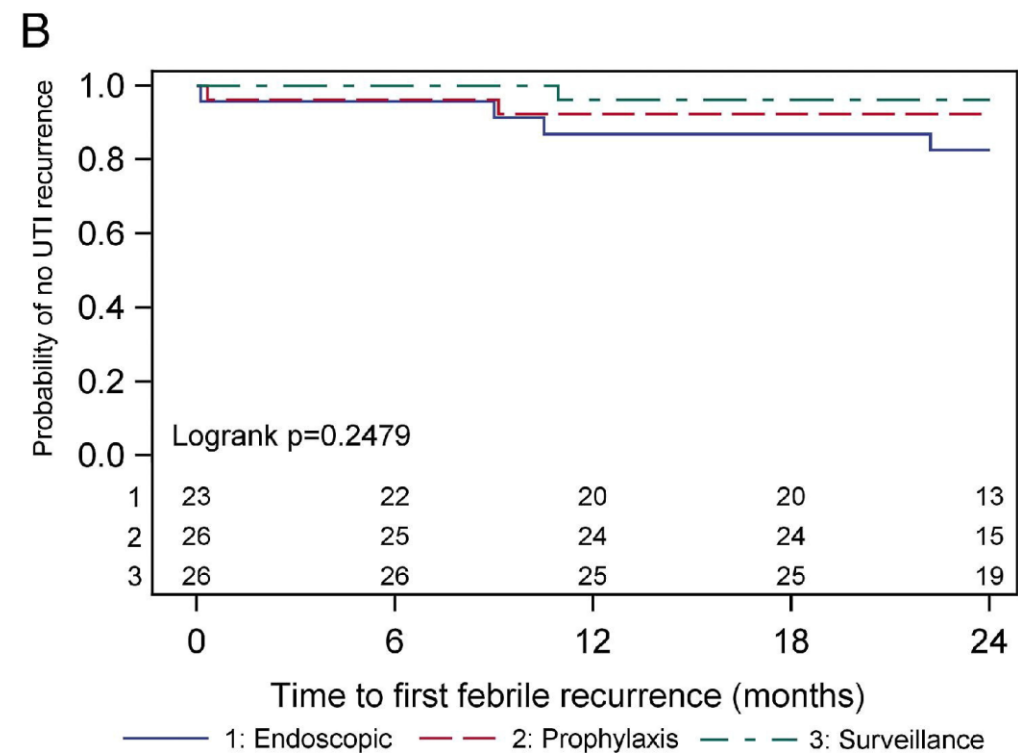
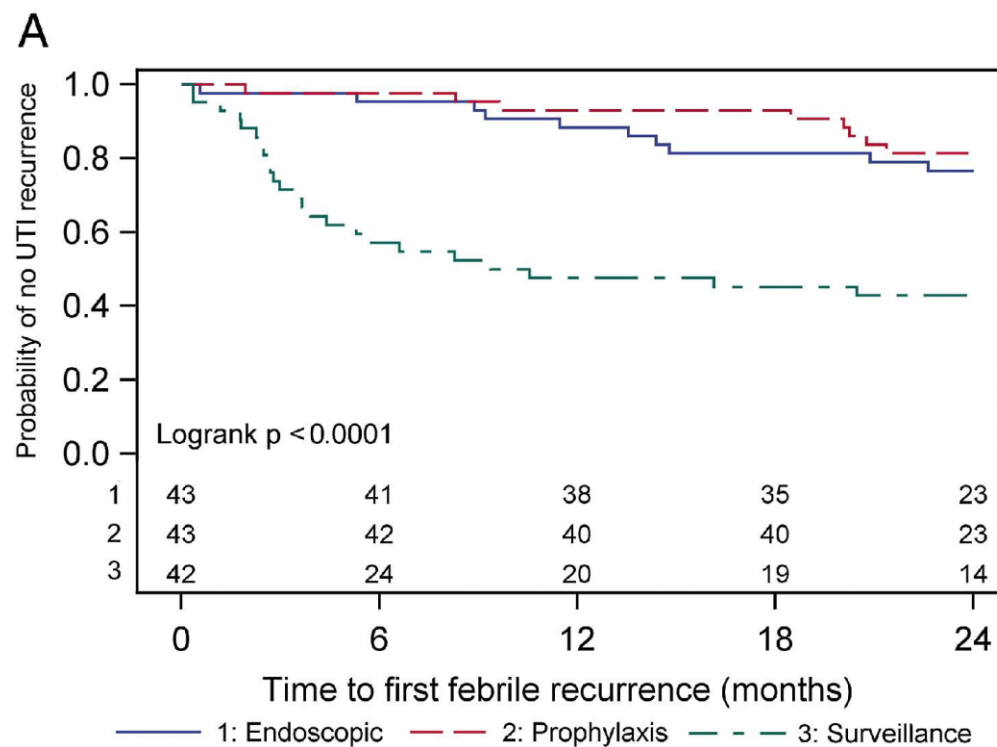
# Swedish Reflux trial



There was a difference in number of girls with recurrence caused by bacteria resistant to trimethoprim between treatment arms ( $p = 0.0489$ ).

Prophylaxis was associated with resistance to trimethoprim compared to surveillance ( $p = 0.038$ ) but there was no such difference between endoscopic treatment and surveillance ( $p = 0.70$ ).







**Table 2.** *Recurrent febrile UTIs in girls during 2-year study by VUR grade and DMSA scan results at study entry*

Study Entry	No. Recurrences					Totals	p Value (Mantel-Haenszel chi-square test)
	0	1	2	3	4		
No. VUR grade:							0.38
III	60	15	12	1	0	88	
IV	26	9	1	2	2	40	
	—	—	—	—	—	—	
Total No.	86	24	13	3	2	128	
No. DMSA scan:							0.44
Normal	44	6	7	1	1	59	
Abnormal	42	18	6	2	1	69	
	—	—	—	—	—	—	
Total No.	86	24	13	3	2	128	

# Sub-inhibitory concentration of antibiotics

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Subinhibitory concentrations of certain antibiotics like ciprofloxacin and gentamicin may paradoxically result in upregulation of bacterial cell surface adhesins in common uropathogens such as *E. coli* and *Staphylococcus saprophyticus*, resulting in denser biofilm formation.

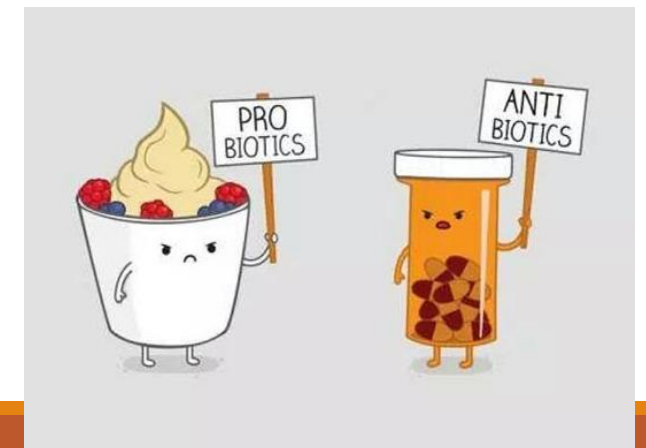
Intraurethral infection of mice with bacteria that were 'primed' with subinhibitory concentrations of antibiotics also resulted in a higher bladder and kidney burden than untreated bacteria and was more likely to cause chronic inflammation by suppression of mucosal immunity.

# Probiotics

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Probiotics are generally thought to exert their effect through:

- 1) production of antimicrobial products such as hydrogen peroxide, bacteriocins, and organic acids that lower the environmental pH and inhibit uropathogen colonization
- 2) competition with uropathogens for iron which is an essential element for several bacterial functions
- 3) occupy the epithelial space to physically resist the adherence of uropathogenic bacteria



# Current evidence

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In one trial, 120 children with established VUR and TMP-SMX prophylaxis in the preceding year were randomly assigned to receive either *Lactobacillus acidophilus* or continue TMP-SMX prophylaxis during the second year of follow-up. The rates of rUTI were similar between the two groups.

In a follow-up trial, 128 infants diagnosed with primary VUR were randomized to receive either the probiotic *Lactobacillus acidophilus* or TMP-SMX for one year. The rates of rUTI in the probiotic and antibiotic prophylaxis groups were not statistically different.

In a retrospective study of 191 infants with acute pyelonephritis and normal urinary tract anatomy, including no VUR, prophylaxis with *Lactobacillus* led to an 8.2% incidence rate of rUTI in the 6 month follow up, which was similar to the 10% rate in the antibiotic group and significantly lower than the 20.6% rUTI rate in no prophylaxis group. All of the infants with rUTI in the antibiotic group were infected with TMP-SMX strains of bacteria, compared to 25% in the probiotic group and 41% in the no-prophylaxis group, further demonstrating the negative consequences of chronic antibiotic prophylaxis.

# Fluoroquinolone-probiotic combination

## Patient Characteristics and Clinical Findings

Patient Number	Age (years)	Gender	Urologic Evaluation	Number of UTIs prior to therapy	Signs and Symptoms reported	Number of recurrences	Follow-up (months)
1	4	F	VCUG -, RUS -	2	Fever + Malodourous urine	0	7
2	5	F	VCUG -, RUS -	10	Fever + Vomiting	1	5
3	6	F	VCUG -, RUS -	4	Fever + Dysuria	0	6
4	6	F	VCUG -, RUS -, MAG3 -	6	Fever + Dysuria	0	10
5	8	F	VCUG -, RUS -, MAG3 -	5	Urgency + Dysuria + Abdominal pain	0	7
6	9	F	RUS -	5	Dysuria + Malodorous urine	2	10
7	10	M	RUS -	5	Fever + Dysuria + Vomiting	0	13
8	10	F	VCUG -, RUS -, MAG3 -, UDS -	8	Fever + Abdominal pain	1	15
9	11	M	VCUG -, RUS -	5	Urgency + Dysuria	0	11
10	13	F	VCUG -, RUS -, UDS -	5	Increased frequency + Dysuria	0	3

\*UDS - Urodynamics, RUS - Renal Ultrasound, VCUG - Voiding Cystourethrogram

# Cranberry juice

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Recent work has shown that cranberry extract prevents adhesion of UPEC to uroepithelial cells in a dose-dependent manner.

This is mediated by two main components of cranberry; **fructose**, which inhibits UPEC adherence by Type 1 fimbriae, and **anthocyanidins** which inhibits adherence by p-fimbriae (pyelonephritis fimbriae).

However, clinical trials on the use of cranberry juice or extracts are inconclusive due to small sample sizes and differences in dose and formulation of cranberry juice or extracts.

# Current evidence

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Of the trials reviewed, four showed a significant reduction in incidence of rUTI. Most of these studies included < 50 patients.

However, one study did enroll 263 children between the ages of 1-16 years with normal urinary anatomy or grade I-II VUR 52. Subjects were given 5 mL/kg, up to 300 mL per day of either cranberry juice or placebo juice in 1 or 2 daily doses for 6 months. The total number of UTI episodes per year was significantly lower in the cranberry group compared to the placebo, but the proportion of subjects that had >1 recurrence was the same.

Antimicrobial prophylaxis had to be started in 3% of subjects in cranberry group compared to 5% among the placebo.

Most studies concur that the use of cranberry juice and preparations are safe for use in all age groups, with the most common side effects being gastrointestinal discomfort.

# Surgical intervention

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**Male circumcision:** Bacterial colonization in the foreskin (prepuce) has been associated with UTIs in male infants less than 3 months of age. In a study that followed 2000 infants, those that were circumcised had a 10-fold lower risk of UTI.

**Renal surgery:** The American Urological Association found the rate of resolution of rUTI was 98% for open surgery and 83% for endoscopic surgery. However, even after surgery, complete resolution of recurrence was dependent on absence of concomitant BBD. Further, children with low grade VUR (I-III) have an approximately 40% chance of spontaneous resolution, especially among children less than 1 yr of age.



# Vaccines

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**SolcoUrovac** is a whole-cell inactivated vaccine used as a vaginal suppository containing 6 *E. coli* strains and 1 strain each of *P. mirabilis*, *M. morganii*, *E. faecalis* and *K. pneumoniae*.

In a phase II clinical trial with this vaccine, 55% percent of the subjects who received the vaccinations were symptom free during the 6 month follow-up period compared to 11% of those in the placebo group.

An intramuscular formulation of SolcoUrovac was used in a trial on 10 otherwise healthy girls (5-11 yrs of age) with rUTI 61. Subjects were vaccinated 3 times at weekly intervals and then received a booster at 6 months. The total number of UTI episodes among all subjects decreased from 34, in the 6 months prior to enrollment, to 13 over a 1 yr follow-up period.

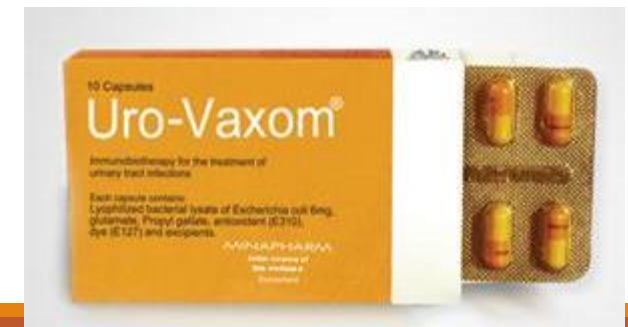
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**Uro-Vaxom** is an oral capsule that contains a lyophilized mixture of membrane proteins from 18 UPEC isolates.

The capsules are taken daily. In a randomized control trial in 120 women, subjects took the vaccine or placebo daily for 3 months and were followed for a further 3 months. By the end of the 6 month study period, subjects in the vaccine group had no episodes of rUTIs.

Uro-Vaxom is currently part of the European Association of Urology guidelines for alternative treatment of UTI in adults.

None of these vaccines are licensed in the US, mainly due to low efficacy, poor adherence to daily regimens and associated toxicity.



# Future studies

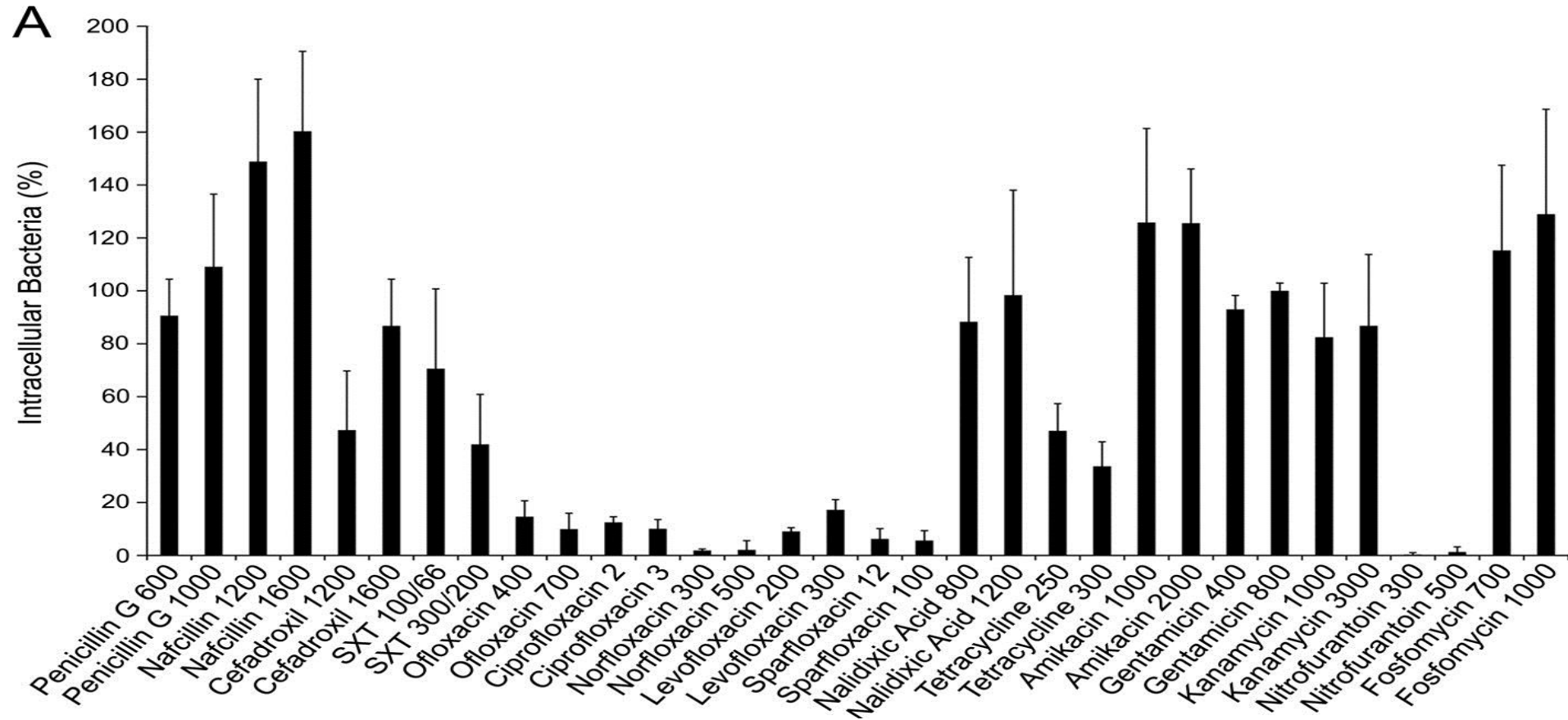
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## **Antibiotics with Intracellular Activity**

Certain classes of antibiotics such as fluoroquinolones and nitrofurantoin have intracellular activity and are therefore capable of eradicating the quiescent colonies of UPEC in a murine UTI model.

The exact mechanism of this intracellular activity is unknown. However, a recent study showed that at least part of the effect exerted by Nitrofurantoin may be due to release of Nitric Oxide, which can easily enter the lipid membrane and impart antimicrobial activity within the cells 65

## Antibiotic effects on intracellular UPEC and host cell cytotoxicity.



Matthew G. Blango, and Matthew A. Mulvey Antimicrob. Agents  
Chemother. 2010;54:1855-1863

Antimicrobial Agents and Chemotherapy

## Vaccines

Ideal vaccination strategies against rUTIs would be to target bacterial factors involved in establishment and maintenance of bladder colonization.

A number of studies have been done on conjugate UTI vaccines targeting the UPEC capsule and O-antigen of the lipopolysaccharide (LPS) and have shown protection against same strain infection in animal models.

Vaccines targeting FimH , the type I pilus adhesin which plays a critical role in bacterial adhesion to urothelial cells, have shown some promise. Studies in monkeys showed significant protection against infection with type I pili expressing UPEC.

This vaccine was originally acquired by Medimmune (Gaithersburg, Maryland, USA) and was previously tested in Phase I and II trials in the early 2000s. The vaccine was safe but showed equivocal efficacy. Thus, the vaccine did not advance to a Phase III trial. Subsequently the vaccine license was acquired by Sequoia Sciences (St. Louis, Missouri, USA) with plans to start Phase III trials using a new adjuvant.

## **Small molecule inhibitors of UPEC pathogenic factors**

They generally act to decrease bacterial virulence and allow the host immune system to effectively eradicate the bacteria.

Cusumano et al identified mannose derivatives, called mannosides, which inhibit the binding of FimH adhesin on type I pili to the mannosylated receptors on the uroepithelial cells by formation of a FimH-oligomannose complex.

These molecules were shown to be effective in treatment of an established chronic infection in a murine model and also showed synergistic activity with conventional antibiotics such as TMP-SMX.

## **Chitosan**

Chitosan is an FDA approved biodegradable linear polysaccharide which was previously used to reduce fat absorption in gut.

Blango et al have also studied the role of chitosan in prevention of rUTIs . When instilled in the bladder in a murine model, chitosan interrupts tight-junctions in the uroepithelium causing rapid differentiation and subsequent sloughing off of superficial cells which harbor IBCs in the acute stages of UTI and later quiescent reservoirs.

A more recent study reported that a combination of chitosan and ciprofloxacin can eradicate the quiescent reservoirs completely.

# Thank you!

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