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Pediatrics 2011;128;e749; originally published online August 28, 2011;
DOI: 10.1542/peds.2011-1332

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Technical Report—Diagnosis and Management of an Initial UTI in Febrile Infants and Young Children

S. Maria E. Finnell, MD, MS, Aaron E. Carroll, MD, MS, Stephen M. Downs, MD, MS, and the Subcommittee on Urinary Tract Infection

KEY WORDS
urinary tract infection, infants, children, vesicoureteral reflux, voiding cystourethrography, antimicrobial, prophylaxis, antibiotic prophylaxis, pyelonephritis

ABBREVIATIONS
UTI—urinary tract infection
VUR—vesicoureteral reflux
VCUG—voiding cystourethrography
CI—confidence interval
RR—risk ratio
RCT—randomized controlled trial
LR—likelihood ratio
SPA—suprapubic aspiration

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1332

doi:10.1542/peds.2011-1332

All technical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

COMPANION PAPERS: Companions to this article can be found on pages 572 and 595, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2011-1330, www.pediatrics.org/cgi/doi/10.1542/peds.2011-1818, and www.pediatrics.org/cgi/doi/10.1542/peds.2011-1330.

abstract

FREE

OBJECTIVES: The diagnosis and management of urinary tract infections (UTIs) in young children are clinically challenging. This report was developed to inform the revised, evidence-based, clinical guideline regarding the diagnosis and management of initial UTIs in febrile infants and young children, 2 to 24 months of age, from the American Academy of Pediatrics Subcommittee on Urinary Tract Infection.

METHODS: The conceptual model presented in the 1999 technical report was updated after a comprehensive review of published literature. Studies with potentially new information or with evidence that reinforced the 1999 technical report were retained. Meta-analyses on the effectiveness of antimicrobial prophylaxis to prevent recurrent UTI were performed.

RESULTS: Review of recent literature revealed new evidence in the following areas. Certain clinical findings and new urinalysis methods can help clinicians identify febrile children at very low risk of UTI. Oral antimicrobial therapy is as effective as parenteral therapy in treating UTI. Data from published, randomized controlled trials do not support antimicrobial prophylaxis to prevent febrile UTI when vesicoureteral reflux is found through voiding cystourethrography. Ultrasonography of the urinary tract after the first UTI has poor sensitivity. Early antimicrobial treatment may decrease the risk of renal damage from UTI.

CONCLUSIONS: Recent literature agrees with most of the evidence presented in the 1999 technical report, but meta-analyses of data from recent, randomized controlled trials do not support antimicrobial prophylaxis to prevent febrile UTI. This finding argues against voiding cystourethrography after the first UTI. *Pediatrics* 2011;128:e749–e770

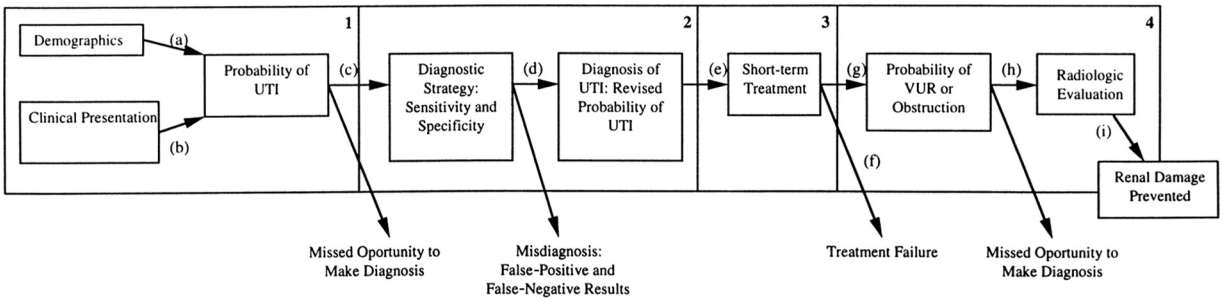

FIGURE 1
Evidence model from the 1999 technical report on the diagnosis and treatment of infants and children with UTIs.

In 1999, the Subcommittee on Urinary Tract Infection of the American Academy of Pediatrics released its guideline on detection, diagnosis, and management for children between 2 and 24 months of age with febrile urinary tract infections (UTIs).[1] The guideline was supported by a technical report[2] that included a critical review of the relevant literature and a cost-effectiveness analysis. Consistent with the policies of the American Academy of Pediatrics, the subcommittee has undertaken a revision of the guideline. This technical report was developed to support the guideline.[3]

The revised technical report was to be based on a selective review of the literature, focusing on changes in the evidence regarding detection, diagnosis, and management of UTIs in these children. The original technical report was designed around an evidence model (Fig 1). Each cell (numbered 1–4) corresponded to a stage in the recognition, diagnosis, or management of UTI. The boxes represented steps the clinician must follow, and the arrows represented the process of moving from one step to the next. Downward arrows represented undesirable consequences in management.[4]

In cell 1, the clinician must combine patient demographic data and other presenting clinical data to arrive at an assessment of the risk of UTI. Failure to do so results in a missed opportunity to make the diagnosis. In cell 2, the clinician must undertake a diagnostic strategy, primarily involving laboratory testing, to arrive at a posterior (posttest) probability of UTI, ruling the diagnosis in or out. Poor test choices or interpretation of results can lead to misdiagnosis. In cell 3, the clinician must choose a treatment for acute UTI; in cell 4, the clinician must consider the possibility of structural or functional anomalies of the urinary tract and diagnose them appropriately to avoid ongoing renal damage.

Implicit in cell 4 is the idea that anomalies of the urinary tract, such as vesicoureteral reflux (VUR) and obstructions, may, if left untreated, lead to significant renal damage, resulting in hypertension or end-stage renal disease. Furthermore, it is assumed that treatment with medical or surgical therapies can prevent these consequences successfully.

The conclusions of the 1999 technical report were that there were high-quality data regarding the prevalence of UTI among febrile infants, the performance of standard diagnostic tests for UTI, and the prevalence of urinary tract abnormalities among children with UTI. The evidence indicating that certain patient characteristics (age, gender, and circumcision status) affected the probability of UTI was weaker. The evidence supporting the relationship between urinary tract abnormalities and future complications, such as hypertension or renal failure, was considered very poor, and the effectiveness of treatments to prevent these complications was not addressed directly but was assumed.

The cost-effectiveness analysis using these data led to the conclusion that diagnosis and treatment of UTI and evaluation for urinary tract anomalies had borderline cost-effectiveness, costing approximately $700 000 per case of hypertension or end-stage renal disease prevented. On the basis of these results, the subcommittee recommended testing all children between 2 and 24 months of age with fever with no obvious source for UTI, by culturing urine obtained through bladder tap or catheterization. As an option for children who were not going to receive immediate antimicrobial treatment, the committee recommended ruling out UTI through urinalysis of urine obtained with any convenient method. The committee concluded that children found to have a UTI should undergo renal ultrasonography and voiding cystourethrography (VCUG) for evaluation for urinary tract abnormalities, most frequently VUR.

Ten years later, the subcommittee has undertaken a review of the technical analysis for a revised guideline. The strategy for this technical report was to survey the medical literature published in the past 10 years for studies of UTIs in young children. The literature was examined for any data that varied significantly from those analyzed in the

first technical report. This survey found an emerging body of literature addressing the effectiveness of antimicrobial agents to prevent recurrent UTI. Therefore, the authors conducted a critical literature review and meta-analysis focused on that specific issue.

METHODS

Surveillance of Recent Literature

The authors searched Medline for articles published in the past 10 years with the medical subject headings "urinary tract infection" and "child (all)." The original search was conducted in 2007, but searches were repeated at intervals (approximately every 3 months) to identify new reports as the guideline was being developed. Titles were reviewed by 2 authors (Drs Downs and Carroll) to identify all articles that were potentially relevant and seemed to contain original data. All titles that were considered potentially relevant by either reviewer were retained. Abstracts of selected articles were reviewed, again to identify articles that were relevant to the guideline and that seemed to contain original data. Review articles that were relevant also were retained for review. Again, all abstracts that were considered potentially relevant by either reviewer were retained. In addition, members of the subcommittee submitted articles that they thought were relevant to be included in the review.

Selected articles were reviewed and summarized by 2 reviewers (Drs Finnell and Downs). The summaries were reviewed, and articles presenting potentially new information were retained. In addition, representative articles reinforcing evidence in the 1999 technical report were retained.

The most significant area of change in the UTI landscape was a new and growing body of evidence regarding the effectiveness of antimicrobial prophylaxis to prevent recurrent infections in children with VUR. To explore this particular issue, a second, systematic, targeted literature search and formal meta-analysis were conducted to estimate the effectiveness of antimicrobial prophylaxis to prevent renal damage in children with VUR. In addition, 1 author (Dr Finnell) and the chairperson of the guideline committee (Dr Roberts) contacted the authors of those studies to obtain original data permitting subgroup analyses.

Targeted Literature Search and Meta-analysis

To examine specifically the effectiveness of antimicrobial prophylaxis to prevent recurrent UTI and pyelonephritis in children with VUR, a formal meta-analysis of randomized controlled trials (RCTs) was conducted. First, a systematic literature review focused on RCTs, including studies in press, was performed.

Inclusion Criteria

RCTs published in the past 15 years (1993–2009) that compared antimicrobial treatment versus no treatment or placebo treatment for the prevention of recurrent UTI and included a minimum of 6 months of follow-up monitoring were included. Published articles, articles in press, and published abstracts were included. There were no language restrictions. To be included, studies needed to enroll children who had undergone VCUG for determination of the presence and grade of VUR. Studies that examined antibiotic prophylaxis versus no treatment or placebo treatment were included.

Outcome Measures

The primary outcome was the number of episodes of pyelonephritis or febrile UTI diagnosed on the basis of the presence of fever and bacterial growth in urine cultures. A secondary outcome was an episode of any type of UTI, including cystitis, nonfebrile UTI, and asymptomatic bacteriuria in addition to the cases of pyelonephritis or febrile UTI.

Search Methods

The initial literature search was conducted on June 24, 2008, and the search was repeated on April 14, 2009. Studies were obtained from the following databases: Medline (1993 to June 2008), Embase (1993 to June 2008), Cochrane Central Register for Controlled Trials, bibliographies of identified relevant articles and reviews, and the Web site www.ClinicalTrials.gov.

The search terms "vesico-ureteral reflux," "VUR," "vesicoureter*," "vesico ureter*," "vesicourethral," or "vesico urethral" and "antibiotic," "anti biotic," "antibacterial," "anti bacterial," "antimicrobial," "anti microbial," "antiinfective," or "anti infective" were used. The asterisk represents the truncation or wild card symbol, which indicates that all suffixes and variants were included. The search was limited to the publication types and subject headings for all clinical trials and included all keyword variants for "random" in Medline and Embase.[5] In addition, the Web site www.ClinicalTrials.gov was searched on May 20, 2010.

The search strategy and the screening of the titles for selection of potentially relevant abstracts were completed by 1 reviewer (Dr Finnell). Two reviewers (Drs Finnell and Downs) screened selected abstracts to identify appropriate articles. Published articles and abstracts that met the inclusion criteria were included in the meta-analysis. Additional information was sought from authors whose articles or abstracts did not contain the information needed for a decision regarding inclusion. The selection process is summarized in Fig 2.

Assessment of Studies

The quality of selected articles and abstracts was assessed with the scoring

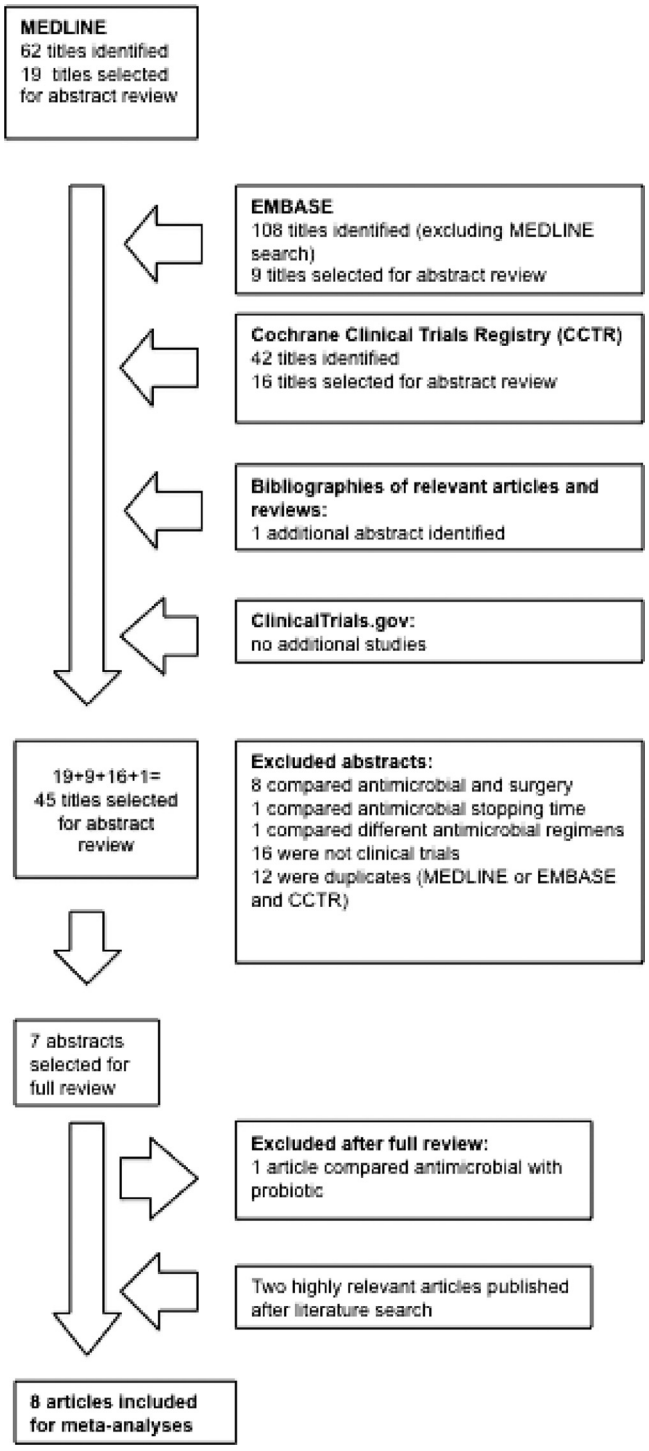

FIGURE 2
Study selection for meta-analyses.

system described by Downs and Black in 1998.[6] Each study received scores (from 2 assessors) on a scale from 0 to 32. Six of the articles and abstracts were included in a first meta-analysis, which evaluated febrile UTI or pyelonephritis as the outcome. A second meta-analysis, which included all studies with the outcome "all UTI," also was conducted.

Meta-analyses

All statistical tests were performed by using Review Manager 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark). The following settings were used for the analyses: dichotomous outcome and Mantel-Haenzel statistical method. Data were analyzed with a random-effects model. When no statistically significant effect and no statistical heterogeneity were detected, data also were analyzed with a fixed-effects model, because that type of analysis is more likely to detect a difference. The effect measure was presented as a risk ratio (RR). The results for the primary outcome (pyelonephritis or febrile UTI) and the secondary outcome (any type of UTI, including cystitis, nonfebrile UTI, and asymptomatic bacteriuria) were calculated as point estimates with corresponding 95% confidence intervals (CIs). Heterogeneity was analyzed by using the Q statistic with a threshold of $P < .05$. The number of studies was insufficient for assessment of publication bias with a funnel plot.

Meta-analyses of Data According to VUR Grade and for Children 2 to 24 Months of Age

The published data on which the meta-analyses were based did not contain subgroup data relevant to the practice guideline. Specifically, some studies did not report outcomes according to the severity of VUR, and some did not report outcomes specific to the age range of interest (2–24 months). Therefore, the committee chairperson contacted the authors of the reports included in the meta-analysis, to obtain original data. Data on recurrence according to VUR grade and for the subgroup of children 2 to 24 months of age were received from the authors, and these data were analyzed in separate meta-analyses.

RESULTS

Surveillance of Recent Literature

The surveillance of recent literature yielded 1308 titles. Of those, 297 abstracts were selected for review. From among the abstracts, 159 articles were selected for full review. The results of this surveillance, as well as the full review and meta-analyses, are organized according to the evidence diagram in Fig 1.

Box 1: Prevalence and Risk Factors for UTI

The Presence of UTI Should Be Considered for Any Child 2 Months to 2 Years of Age With Unexplained Fever

The previous technical report described a very consistent UTI prevalence of 5% among children 2 to 24 months of age with a fever without obvious source. In 1996, Hoberman et al[7] conducted a study of urine diagnostic tests with a cohort of 4253 infants with fever and found a prevalence of 5%. Similarly, in a 1999 cohort study of 534 children 3 to 36 months of age with a temperature of more than 39°C and no apparent source of fever, UTI prevalence was determined to be 5%.[8] In a 1998 cohort study of 2411 children (boys and girls <12 months of age and girls 12–24 months of age) seen in the emergency department with a temperature of more than 38.5°C, Shaw et al[9] determined the prevalence of UTI to be 3.3%. Because 84% of those children were black, this estimate may be low for the general population (see below). In a meta-analysis of 14 studies, the pooled prevalence of UTI was 7% (95% CI: 5.5%–8.4%) among febrile children 0 to 24 months of age, of both genders, with or without additional symptoms of UTI.[10] In the 6- to 12-month age group, however, the prevalence was 5.4%; in the 12- to 24-month age group, the prevalence was 4.5%. Taken together, these estimates are consistent with a pooled prevalence of 5% determined in earlier studies.

The previous technical report examined the effects of age, gender, and circumcision status on the prevalence of UTI. The conclusion was that boys more than 1 year of age who had been circumcised were at sufficiently low risk of UTI (<1%) that evaluation of this subpopulation would not be cost-effective. New work confirms an approximately threefold to fourfold decreased risk of UTI among circumcised boys.[10] The difference seems to be greater for younger children.[11] Additional clinical characteristics were shown more recently to affect the risk of UTI among febrile infants and children. From a study by Shaikh et al,[12] a set of likelihood ratios (LRs) for various risk factors for UTI was derived (Table 1).

A simplified way to examine the data on boys from Shaikh et al[12] is first to exclude boys with a history of UTI, because the guideline addresses only first-time UTIs, and to exclude those with ill appearance, because they are likely to require antimicrobial agents, in which case a urine specimen would be required. Finally, boys with and without circumcision should be considered separately. This leaves 4 risk factors for boys who present with fever, namely, temperature above 39°C, fever for more than 24 hours, no apparent fever source, and nonblack race. All 4 have similar LRs. If 2 assumptions are made, then the decision rule can be simplified. The first assumption is that, as a first approximation, each risk factor has a positive LR of 1.4 and a negative LR of 0.7. The second assumption is that the presence of each risk factor is conditionally independent of the others, given the presence or absence of UTI. With these reasonable assumptions, Table 2 applies to boys with no previous history of UTI

TABLE 1 LRs and Posttest Probabilities of UTI for Infant Boys According to Number of Findings Present

Finding	LR		Posttest Probability, %					
			All Boys		Circumcised Boys		Uncircumcised Boys	
	Positive	Negative	After Positive Results	After Negative Results	After Positive Results	After Negative Results	After Positive Results	After Negative Results
Uncircumcised	2.8	0.33	5.9	0.7	—	—	—	—
History of UTI	2.6	0.96	5.5	2.1	1.8	0.7	14.0	5.7
Temperature of >39°C	1.4	0.76	3.1	1.7	1.0	0.5	8.1	4.5
Fever without apparent source	1.4	0.69	3.1	1.5	1.0	0.5	8.1	4.1
Ill appearance	1.9	0.68	4.1	1.5	1.3	0.5	10.6	4.1
Fever for >24 h	2.0	0.9	4.3	2.0	1.4	0.6	11.1	5.3
Nonblack race	1.4	0.52	3.1	1.2	1.0	0.4	8.1	3.2

TABLE 2 LRs and Posttest Probabilities of UTI for Febrile Infant Boys According to Number of Findings Present

No. of Risk Factors	LR	Posttest Probability, %		
		All Boys	Uncircumcised	Circumcised
0	0.34	0.8	2.1	0.2
1	0.69	1.5	4.1	0.5
2	1.37	3.0	7.9	1.0
3	2.74	5.8	14.7	1.9
4	5.49	11.0	25.6	3.7

Risk factors: temperature above 39°C, fever for more than 24 hours, no apparent fever source, and nonblack race.

TABLE 3 LRs and Posttest Probabilities of UTI for Febrile Infant Girls According to Number of Findings Present (Prospective Original Study)

Cutoff Value, No. of Factors	LR		Posttest Probability, %	
	Positive	Negative (Approximate)	Below Cutoff Value	At or Above Cutoff Value
1	1.04	0.20	0.8	5.1
2	1.35	0.17	0.8	6.5
3	2.5	0.42	2.1	11.4
4	9.4	0.79	3.9	33.0
5	15.8	0.95	4.7	45.0

Risk factors: less than 12 months of age, white race, temperature > 39°C, fever for at least 2 days, and absence of another source of infection.

TABLE 4 LRs and Posttest Probabilities of UTI for Febrile Infant Girls According to Number of Findings Present (Retrospective Validation Study)

No. of Findings	LR	Posttest Probability, %
0 or 1	1.02	0.8
2	1.10	0.9
3	1.26	1.0
4	3.04	2.4
5	2.13	1.7

Risk factors: less than 12 months of age, white race, temperature > 39°C, fever for at least 2 days, and absence of another source of infection.

and do not appear ill. The LR is calculated as LR = $(1.4)^p \times (0.7)^n$, where p is the number of positive findings and n is the number of negative findings. This assumes that the clinician has assessed all 4 risk factors. It should be noted that, for uncircumcised boys, the risk of UTI never decreases below 2%. For circumcised boys, the probability exceeds 1% if there are 2 or more risk factors.

Other studies have shown that the presence of another, clinically obvious source of infection,[13] particularly documented viral infections,[14] such as respiratory syncytial virus infections,[15] reduces the risk of UTI by one-half. In a series of studies conducted by Gorelick, Shaw, and others,[9,16,17] male gender, black race, and no history of UTI were all found to reduce the risk. The authors derived a prediction rule specifically for girls, with 95% sensitivity and 31% specificity. In a subsequent validation study, they confirmed that these findings had predictive power, but the validation study used a weaker, retrospective, case-control design, compared with the more-robust, prospective, cohort design of the original derivation study. On the basis of the earlier cohort study and starting with a baseline risk of 5%, a child scoring low on the prediction rule would have a slightly less than 1% risk of UTI. To score this low on the prediction rule, a young girl would have to exhibit no more than 1 of the following features: less than 12 months of age, white race, temperature of more than 39°C, fever for at least 2 days, or absence of another source of infection.

However, those authors evaluated their decision rule with several different cutoff points, to determine the score below which the risk of UTI decreased below a test threshold of 1%. Unfortunately, the published article did not include the set of negative LRs needed to reproduce the posterior probabilities.[17] However, it was possible to approximate them through extrapolation from the receiver operating characteristic curve presented. On the basis of these estimated negative LRs and the positive LRs provided in the article,[17] Table 3 was derived. For each cutoff value in the number of risk factors, Table 3 shows the posterior probability for children with fewer than that number of risk factors (below the cutoff value) and for those with that number of risk factors *or more*. Therefore, the posttest probability is not the risk of UTI for children with exactly that number of risk factors. Similar results could be derived from the validation study and are shown in Table 4. However, because the second study had a weaker design, the values in Table 3 are more reliable.

These studies provide criteria for practical decision rules that clinicians can use to select patients who need urine samples for analysis and/or culture. They do not establish a threshold or maximal risk of UTI above which a urine sample is needed. However, in surveys of pediatricians, Roberts et al[18] found that only 10% of clinicians thought that a urine culture is indicated if the probability of UTI is less than 1%. In addition, the cost-effectiveness analysis published in the 1999 technical report set a threshold of 1%. However, circumstances such as risk of loss to follow-up monitoring or other clinician concerns may shift this threshold up or down.

TABLE 5 List of Test Characteristics of Diagnostic Tests for UTI Reported in 1999 Technical Report[2]

Test	Sensitivity, %			Specificity, %		
	Range	Median	Mean	Range	Median	Mean
Leukocyte esterase test	67–94	84	83	64–92	77	78
Nitrite test	15–82	58	53	90–100	99	98
Blood assessment	25–64	53	47	60–89	85	78
Protein assessment	40–55	53	50	67–84	77	76
Microscopy, leukocytes	32–100	*78*	73	45–98	87	81
Microscopy, bacteria	16–99	88	81	11–100	93	83
Leukocyte esterase or nitrite test	90–100	92	93	58–91	70	72
Any positive test results in urinalysis	99–100	100	99.8	60–92	63	70

TABLE 6 Test Characteristics of Laboratory Tests for UTI in Children

Study	Test	Population	*n*	Sensitivity, %	Specificity, %
Lockhart et al[19] (1995)	Leukocyte esterase or nitrite test results positive	Prospective sample, <6 mo of age, ED	207	67	79
	Any bacteria with Gram-staining				
Hoberman et al[7] (1996)	>10 white blood cells per counting chamber or any bacteria per 10 oil emersion fields	<2 y of age, 95% febrile, ED	4253	96	93
Shaw et al[9] (1998)	Enhanced urinalysis	Infants <12 mo of age and girls <2 y of age, ≥38.5°C, ED	3873	94	84
	Dipslide or standard urinalysis			83	87
Lin et al[20] (2000)	Hemocytometer, ≥10 cells per μL	Systematic review, febrile infants hospitalized, febrile UTI	NA	83	89

ED indicates emergency department; NA, not applicable.

Box 2: Diagnostic Tests for UTI

The 1999 technical report reviewed a large number of studies that described diagnostic tests for UTI. The results are summarized in Table 5. This updated review of the literature largely reinforced the findings of the original technical report.

More-recent work compared microscopy, including the use of hemocytometers and counting chambers (enhanced urinalysis), with routine urinalysis or dipslide reagents (Table 6). Lockhart et al[19] found that the observation of any visible bacteria in an uncentrifuged, Gram-stained, urine sample had better sensitivity and specificity than did combined dipslide leukocyte esterase and nitrite test results. Hoberman et al[7] in 1996 and Shaw et al[20] in 1998 both evaluated enhanced urinalysis, consisting of more than 10 white blood cells in a counting chamber or any bacteria seen in 10 oil emersion fields; they found sensitivity of 94% to 96% and specificity of 84% to 93%. In 2000, Lin et al[21] found that a count of at least 10 white blood cells per μL in a hemocytometer was less sensitive (83%) but quite specific (89%). Given the sensitivity of enhanced urinalysis, the probability of UTI for a typical febrile infant with a previous likelihood of UTI of 5% would be reduced to 0.2% to 0.4% with negative enhanced urinalysis results.

Obtaining a Urine Sample

In the UTI practice parameters from 1999, the subcommittee defined the gold standard of a UTI to be growth of bacteria on a culture of urine obtained through suprapubic aspiration (SPA). In the previous technical report, SPA was reported to have success rates ranging from 23% to 90%,[22–24] although higher success rates have been achieved when SPA is conducted under ultrasonographic guidance.[25,26] SPA is considered more invasive than catheterization and, in RCTs from 2006[27] and 2010,[28] pain scores associated with SPA were significantly higher than those associated with catheterization. This result was found for both boys and girls. Similar to previous studies, these RCTs also revealed lower success rates for SPA (66% and 60%), compared with catheterization (83% and 78%).[27,28] In comparison with SPA results, cultures of urine specimens obtained through catheterization are 95% sensitive and 99% specific.[7,11,12]

Cultures of bag specimens are difficult to interpret. In the original technical report, sensitivity was assumed to be 100% but the specificity of bag cultures was shown to range between 14% and 84%.[2] Our updated surveillance of the literature did not show that these numbers have improved.[29–33] One article suggested that a new type of collection bag may result in improved specificity,[34] but that study was not controlled. With a prevalence of 5% and specificity of 70%, the positive predictive value of a positive culture result for urine obtained in a bag would be 15%. This means that, of all positive culture results for urine obtained in a bag, 85% would be false-positive results.

Box 3: Short-term Treatment of UTIs

General Principles of Treatment

Published evidence regarding the short-term treatment of UTIs supports 4 main points. First, complications, such as bacteremia or renal scarring, are sufficiently common to necessitate early, thorough treatment of febrile UTIs in infants.[35] Second, treatment with orally administered antimicrobial agents is as effective as parenteral therapy.[36,37] Third, bacterial sensitivity to antimicrobial agents is highly variable across time and geographic areas, which suggests that therapy should be guided initially by local sensitivity patterns and should be adjusted on the basis of sensitivities of isolated pathogens.[38,39] Fourth, meta-analyses have suggested that shorter durations of oral therapy may not have a disadvantage over longer courses for UTIs. However, those studies largely excluded febrile UTI and pyelonephritis.[40]

Experimental and Clinical Data Support the Concept That Delays in the Institution of Appropriate Treatment for Pyelonephritis Increase the Risk of Renal Damage

The 1999 technical report cited evidence that febrile UTIs in children less

TABLE 7 Recent Studies Documenting the Prevalence of VUR Among Children With UTI

Study	Description	*n*	Prevalence, %
Sargent and Stringer[50] (1995)	Retrospective study of first VCUG for UTI in children 1 wk to 15 y of age	309	30
Craig et al[51] (1997)	Cross-sectional study of children <5 y of age with first UTI	272	28
McDonald et al[52] (2000)	Retrospective chart review of children with VCUG after UTI	176	19
Oostenbrink et al[53] (2000)	Cross-sectional study of children <5 y of age with first UTI	140	26
Mahant et al[54] (2001)	Retrospective chart review of children with VCUG after UTI	162	22
Mahant et al[55] (2002)	Retrospective review of VCUG in children <5 y of age admitted with first UTI	162	22
Chand et al[56] (2003)	Retrospective review of VCUG or radionuclide cystogram in children <7 y of age	15 504	35
Fernandez-Menendez et al[44] (2003)	Prospective cohort study of 158 children <5 y of age (85% < 2 y) with first UTI	158	22
Camacho et al[41] (2004)	Prospective cohort study of children 1 mo to 12 y of age (mean age: 20 mo) with first febrile UTI	152	21
Hansson et al[57] (2004)	Retrospective cross-sectional study of children <2 y of age with first UTI	303	26
Pinto[58] (2004)	Retrospective chart review of first VCUG for UTI in children 1 mo to 14 y of age	341	30
Zamir et al[59] (2004)	Cohort study of children 0–5 y of age hospitalized with first UTI	255	18

than 2 years of age are associated with bacterial sepsis in 10% of cases.[35] Furthermore, renal scarring is common among children who have febrile UTIs. The risk is higher among those with higher grades of VUR[41] but occurs with all grades, even when there is no VUR. Although it was not confirmed in all studies,[42,43] older work[2] and newer studies[44] demonstrated an increased risk of scarring with delayed treatment. Children whose treatment is delayed more than 48 hours after onset of fever may have a more than 50% higher risk of acquiring a renal scar.

Oral Versus Intravenous Therapy

In a RCT from 1999, Hoberman et al[36] studied children 1 to 24 months of age with febrile UTIs. They compared 14 days of oral cefixime treatment with 3 days of intravenous cefotaxime treatment followed by oral cefixime treatment to complete a 14-day course. The investigators found no difference in outcomes between children who were treated with an orally administered, third-generation cephalosporin alone and those who received intravenous treatment.

In a Cochrane review, Hodson et al[37] evaluated studies with children 0 to 18 years of age, examining oral versus intravenous therapy. No significant differences were found in duration of fever (2 studies; mean difference: 2.05 hours [95% CI: −0.84 to 4.94 hours]) or renal parenchymal damage at 6 to 12 months (3 studies; RR: 0.80 [95% CI: 0.50–1.26]) between oral antimicrobial therapy (10–14 days) and intravenous antimicrobial treatment (3 days) followed by oral antimicrobial treatment (11 days).

Duration of Therapy

In the 1999 technical report, data slightly favoring longer-duration (7–10 days) over shorter-duration (1 dose to 3 days) antimicrobial therapy for pediatric patients with UTIs were presented.[2] Since then, several meta-analyses with different conclusions have been published on this topic.[40,45,46] A 2003 Cochrane review addressing the question analyzed studies that examined the difference in rates of recurrence for positive urine cultures after treatment.[40] It compared short (2–4 days) and standard (7–14 days) duration of treatment for UTIs and found no significant difference in the frequency of bacteriuria after completion of treatment (8 studies; RR: 1.06 [95% CI: 0.64–1.76]). Although the authors of the review did not exclude studies of children with febrile UTIs or pyelonephritis, each individual study included in the meta-analysis had already excluded such children. To date, there are no conclusive data on the duration of therapy for children with febrile UTIs or pyelonephritis.

Proof of Cure

Data supporting routine repeat cultures of urine during or after completion of antimicrobial therapy were not available for the 1999 technical report. Retrospective studies did not show "proof of bacteriologic cure" cultures to be beneficial.[47,48] Studies demonstrating that clinical response alone *ensures* bacteriologic cure are not available.

Box 4: Evaluation and Management of Urinary Tract Abnormalities

Prevalence of VUR

Several cohort studies published since the 1999 technical report provide estimates of the prevalence of VUR of various grades among infants and children with UTIs (Table 7). Overall, these estimates are reasonably consistent with those reported in earlier studies, although the grades of reflux are now reported more consistently, by using the international system of radiographic grading of VUR.[49]

The prevalence of VUR among children in these studies varies between 18% and 35%. The weighted average prevalence is 34%, but this is largely driven by the enormous retrospective study by Chand et al.[56] Most studies report a rate of 24% or less, which is less than the estimate of VUR prevalence in the 1999 technical report.

Data on the prevalence of VUR among children *without* a history of UTI do not

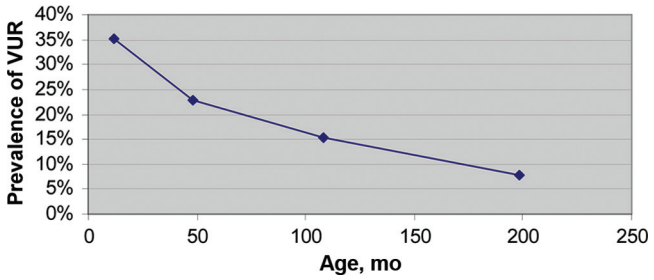

FIGURE 3
Prevalence of VUR as a function of the midpoint of each age stratum, as reported by Chand et al.[56]

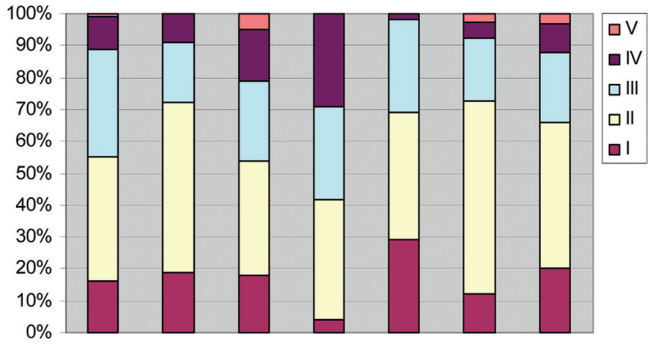

FIGURE 4
Distribution of reflux grades among children with VUR.[41,44,51,56,57,62,63]

exist. Using a retrospective approach and existing urine culture data, Hannula and Ventola and colleagues,[60,61] in 2 separate publications, found similar rates of prevalence of any grade of VUR among children with proven (37.4%) or certain (36%) UTI versus false (34.8%) or improbable (36%) UTI. These results suggest that VUR is prevalent even among children without a history of UTI.

The prevalence of VUR decreases with age. This was approximated by analysis across studies in the 1999 technical report. Since then, Chand et al[56] reported the prevalence VUR within age substrata of their cohort. Figure 3 shows the prevalence of VUR plotted as a function of the midpoint of each age stratum.

Seven studies reported the prevalence of different grades of reflux, by using the international grading system.[41,44,51,56,57,62,63] The distributions of different reflux grades among children who had VUR are shown in Fig 4. There is significant variability in the relative predominance of each reflux grade, but grades II and III consistently are the most common. With the exception of the study by Camacho et al,[41] all studies showed grades IV and V to be the least frequent, and grade V accounted for 0% to 5% (weighted average: 3%) of reflux. With that value multiplied by the prevalence of VUR among young children with a first UTI, we would expect grade V reflux to be present in <1% of children with a first UTI.

It has been suggested that the risk of VUR and, more specifically, high-grade VUR may be higher for children with recurrent UTI than for children with a first UTI. Although it was not tested directly in the studies reviewed, this idea can be tested and the magnitude of the effect can be estimated from the data found in the literature search for this meta-analysis.[64–70] These data clearly demonstrate that the risk of UTI recurrence is associated with VUR (Fig 5). Furthermore, this relationship allows the likelihood of each grade of reflux (given that a UTI recurrence has occurred) to be estimated by using Bayes' theorem, as follows:

$$p(\mathrm{VUR}_i|\mathrm{UTI}) = \frac{p(\mathrm{UTI}|\mathrm{VUR}_i) \times p(\mathrm{VUR}_i)}{\sum_{i=0}^{V} p(\mathrm{UTI}|\mathrm{VUR}_i) \times p(\mathrm{VUR}_i)},$$

where $p(\mathrm{UTI}|\mathrm{VUR}_i)$ refers to the probability of VUR of grade i given the recurrence of UTI. If it is assumed that the conditional probabilities remain the same with second or third UTIs, then Bayes' theorem can be reapplied for a third UTI as well.

By using estimates of p(UTI VUR) (Fig 5) and the previously determined distri-

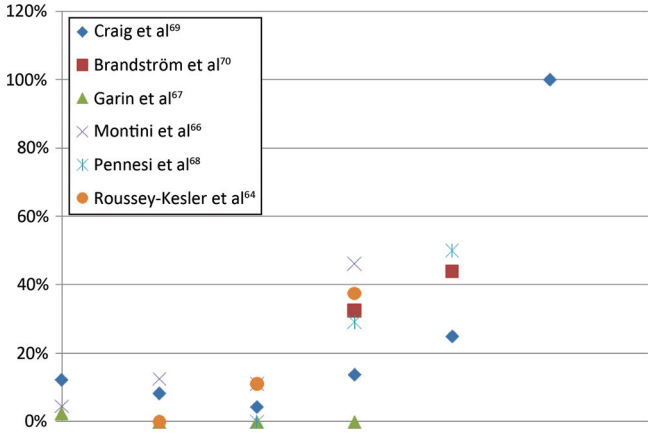

FIGURE 5
Probability of a recurrent febrile UTI as a function of VUR grade among infants 2 to 24 months of age in the control groups of the studies included in meta-analyses.[64,66–70]

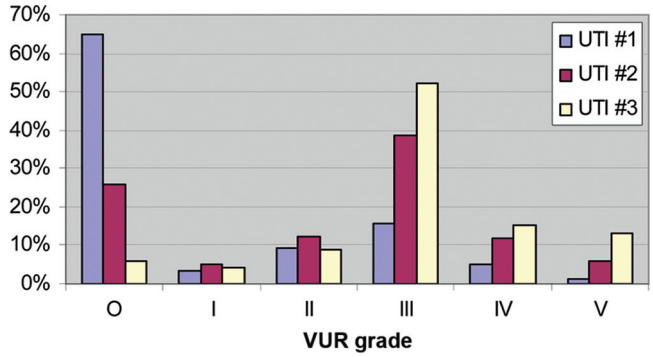

FIGURE 6
Distribution of VUR grades after different numbers of UTIs.

butions of VUR grades (Fig 4), a very approximate estimate of the distribution of VUR grades after the first, second, and third UTI can be made (Fig 6). The likelihood that there is no VUR decreases rapidly. Conversely, the likelihood of VUR grades III to V increases rapidly. The risk of grades I and II changes little.

Ultrasonography

Ultrasonography is used as a noninvasive technique to identify renal abnormalities in children after UTI. The sensitivity of the test varies greatly and has been reported to be as low as 5% for detection of renal scarring[71–73] and 10% for detection of VUR.[74] However, most studies report moderate specificity.

One possible reason for a decrease in specificity is that, in animal models, *Escherichia coli* endotoxin has been shown to produce temporary dilation of the urinary tract during acute infection.[75] Therefore, use of routine ultrasonography for children with UTIs during acute infection may increase the false-positive rate. However, no human data are available to confirm this hypothesis.

Ultrasonography is used during acute infection to identify renal or perirenal abscesses or pyonephrosis in children who fail to experience clinical improvement despite antimicrobial therapy. The sensitivity of ultrasonography for such complications is thought to be very high, approaching 100%.[76] Therefore, ultrasonography in the case of a child with a UTI who is not responding to therapy as expected can be very helpful in ruling out these infectious complications.

Ultrasonography also is advocated for screening for renal abnormalities such as hydronephrosis, suggesting posterior urethral valves, ureteropelvic junction obstruction, or ureteroceles. The evidence model illustrates the expected outcomes from routine ultrasonography of the kidneys, ureters, and bladder after the first febrile UTI in infants and young children (Fig 7). The model is based on the study results documented in Tables 8 and 9 and a strategy of performing kidney and bladder ultrasonography for all infants with UTIs. The numbers are not exact for 2 reasons, namely, (1) study populations vary and do not always precisely meet the definitions of 2 to 24 months of age and febrile without another fever source and, (2) even within similar populations, reported rates vary widely.

Ultrasonography yields ~15% positive results. However, it has a ~70% false-negative rate for reflux, scarring, and other abnormalities. Limited data exist regarding the false-negative rate for high-grade VUR (grade IV and V), but the studies reviewed presented 0% to 40% false-negative rates for detection of grade IV reflux through ultrasonography.[59,74] Among the 15% of results that are positive, between 1% and 24% are false-positive results. Of the true-positive results, ~40% represent some dilation of the collecting system, such as would be found on a VCUG; 10% represent abnormalities that are potentially surgically correctable (eg, ureteroceles or ureteropelvic junction obstruction). Approximately one-half represent findings such as horseshoe kidneys or renal scarring, for which there is no intervention but which might lead to further evaluations, such as technetium-99m–labeled dimercaptosuccinic acid renal scintigraphy. The 40% with dilation of the collecting system are problematic. This represents only a small fraction of children (15% × 88% × 40% = 5%) with first UTIs who would be expected to have VUR before ultrasonography. Ultrasonography does not seem to be enriching for this population (although ultrasonography might identify a population with higher-grade VUR).

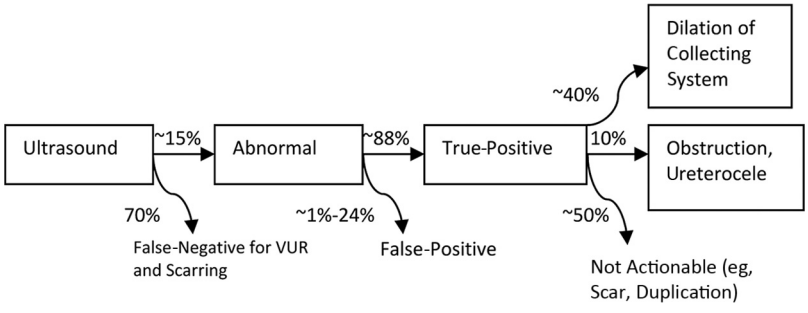

FIGURE 7
Evidence model for ultrasonography after a first UTI.

TABLE 8 Summary of Ultrasonography Literature

Study	*n*/*N* (%)	Comments
False-negative rate		
Scarring		
Smellie et al[73] (1995)	7/20 (35)	
Barry et al[77] (1998)	23/170 (14)	
Moorthy et al[71] (2004)	219/231 (95)	
Sinha et al[78] (2007)	61/79 (77)	Reported as renal units
Montini et al[79] (2009)	33/45 (73)	
VUR		
Smellie et al[73] (1995)	21/36 (58)	
Mahant et al[55] (2002)	14/35 (40)	
Hoberman et al[74] (2003)	104/117 (90)	
Zamir et al[59] (2004)	38/47 (81)	
Montini et al[79] (2009)	48/66 (73)	
Other		
Smellie et al[74] (1995)	5/5 (100)	Duplex kidney
False-positive rate		
Scarring		
Barry et al[77] (1998)	11/478 (2)	
Moorthy et al[71] (2004)	12/699 (1.7)	
Sinha et al[78] (2007)	9/870 (1)	
Monitini et al[79] (2009)	26/255 (10)	
VUR		
Smellie et al[73] (1995)	2/12 (17)	Normal VCUG, DMSA, and IVU results
Mahant et al[55] (2002)	30/127 (24)	
Hoberman et al[74] (2003)	17/185 (10)	
Zamir et al[59] (2004)	27/208 (13)	
Other		
Giorgi et al[80] (2005)	21/203 (10)	

IVU indicates intravenous urography; DMSA, dimercaptosuccinic acid.

Prenatal Ultrasonography

Urinary tract abnormalities also may be identified during prenatal ultrasonography,[85–87] which theoretically would decrease the number of new abnormalities found through later ultrasonography.[81] However, the extent to which normal prenatal ultrasonographic findings decrease the need for later studies remains in doubt.

Miron et al[88] studied 209 children who underwent ultrasonography prenatally and again after a UTI. They found that, among 9 children with abnormal ultrasonographic results after UTI, 7 had normal prenatal ultrasonographic results. These cases included 3 cases of hydronephrosis, 3 cases of moderate dilation, and 1 case of double collecting system. Similarly, in a study by Lakhoo et al[89] in 1996, 22 of 39 children with UTIs had normal prenatal ultrasonographic results but "abnormal" post-UTI ultrasonographic results; the abnormalities were not described. These studies suggest that normal prenatal ultrasonographic findings may not be sufficient to obviate the need for additional studies if a UTI occurs in infancy.

Results of Targeted Literature Review and Meta-analysis on Prophylaxis to Prevent Recurrent UTI

Study Identification

For the meta-analysis of studies on the effectiveness of antimicrobial agents to prevent recurrent UTI in children with VUR, we reviewed a total of 213 titles from our primary literature search. Of those, 45 were retained for abstract review on the basis of the title, of which 7 were selected for full review. Six of the studies met the inclusion criteria. Figure 2 summarizes the selection process.

Thirty-eight abstracts were excluded before full review (Fig 2). Eight of those studies were RCTs comparing prophylactic antimicrobial agent use with some type of surgical intervention. None of those studies included a placebo arm.[90–97] One study compared different lengths of antimicrobial prophylaxis.[98] Another study compared different antimicrobial regimens but did not include a placebo arm.[99] Sixteen studies were determined, on closer inspection, to be not clinical trials but prospective cohort studies, reviews, systematic reviews, or meta-analyses. Twelve studies were found twice, either in Medline or Embase and the Cochrane Clinical Trials Registry.

One article was excluded after full review (Fig 2). That study compared prophylactic antimicrobial agent use with probiotic use.[65] The study was not included in the meta-analysis, but the results are described separately.

There are RCTs of antimicrobial prophylaxis that are older than 15 years. In 4 studies from the 1970s, a total of 179 children were enrolled.[100–103] Less than 20% of those children had VUR. Because of limited reporting of results in that subgroup, those older studies were not included in the analyses.

Two additional RCTs comparing antimicrobial prophylaxis and placebo treatment for children were published in October 2009.[69,70] The first trial enrolled children 0 to 18 years of age after a first UTI, with 2% of enrolled children (12 of 576 children) being more than 10 years of age. The second trial enrolled children diagnosed as having VUR after a first UTI (194 [96%] of 203 children) or after prenatal ultrasonography (9 [4%] of 203 children), who were then assigned randomly to receive antimicrobial prophylaxis, surveillance, or endoscopic therapy, at 1 to 2 years of age. The majority of these children (132 children [65%]) had been diagnosed as having VUR before 1

TABLE 9 Distribution of Positive Ultrasonographic Findings

Study	*n*/*N* (%)
Alon and Ganapathy[62] (1999)	19/124 (15)
Minimal unilateral changes	
VUR	2 (1.6)
Normal VCUG findings	2 (1.6)
Resolved on repeat study	2 (1.6)
Not monitored further	3 (2.4)
Major changes	8 (6.5)
VUR	1 (1.6)
Normal findings	1 (1.6)
Posterior urethral valve	1 (1.6)
Hydroureternephrosis	1 (1.6)
Gelfand et al[81] (2000)	141/844 (16.7)
Bladder wall thickening	31 (3.7)
Hydroureter	6 (0.7)
Parenchymal abnormalities	42 (5.0)
Pelvocalyceal dilation	27 (3.2)
Renal calculus	1 (0.1)
Simple renal cyst	1 (0.1)
Urethelial thickening	31 (3.7)
Jothilakshmi et al[82] (2001)	42/262 (16)
Duplex kidney	3 (1)
Crossed renal ectopia	1 (0.38)
Horseshoe kidney	1 (0.38)
Hydronephrosis	5 (1.9)
Megaureter	6 (2.3)
Polycystic kidney	1 (0.38)
Pelviureteric junction obstruction	1 (0.38)
Posterior urethral valve	2 (0.76)
Renal calculus	3 (0.01)
Rotated kidney	2 (0.76)
Ureterocele	2 (0.76)
VUR	7 (2.7)
Hoberman et al[74] (2003)	37/309 (12)
Dilated pelvis	13 (4.2)
Pelvocaliectasis	12 (3.9)
Hydronephrosis	2 (0.6)
Dilated ureter	9 (2.9)
Double collecting system	3 (1.0)
Extrarenal pelvis	1 (0.3)
Calculus	1 (0.3)
Zamir et al[59] (2004)	36/255 (14.1)
Mild unilateral pelvis dilation	32 (12.5)
Moderate unilateral pelvis dilation	1 (0.04)
Enlargement kidney	1 (0.04)
Small renal cyst	1 (0.04)
Double collecting system and severe hydronephrosis	1 (0.04)
Jahnukainen et al[83] (2006)[a]	23/155 (14.8)
Hydronephrosis	8 (5)
Double collecting system	11 (7)
Multicystic dysplasia	1 (0.6)
Renal hypoplasia	1 (0.6)
Solitary kidney	1 (0.6)
Horseshoe kidney	1 (0.6)
Huang et al[84] (2008)	112/390 (28.7)
Nephromegaly	46 (11.8)
Isolated hydronephrosis	20 (5.1)
Intermittent hydronephrosis	3 (0.8)
Hydroureter	8 (2.1)
Hydroureter and hydronephrosis	3 (0.8)
Thickened bladder wall	11 (2.8)
Small kidneys	8 (2.1)
Simple ureterocele	5 (1.3)
Double collecting systems	4 (1.0)
Increased echogenicity	3 (0.8)
Horseshoe kidney	1 (0.3)
Montini et al[79] (2009)	38/300 (13)
Dilated pelvis, ureter, or pelvis and calyces	12 (4)
Renal swelling or local parenchymal changes	10 (3.3)
Increased bladder wall or pelvic mucosa, thickness	6 (2)
Other	10 (3.3)

[a] Hospitalized children with UTI.

year of age and thus had been receiving prophylaxis before random assignment. These studies were included in the meta-analysis.

Description of Included Studies

Table 10 presents characteristics of the 8 included studies.[64,66–70,104,105] Four studies enrolled children after diagnosis of a first episode of pyelonephritis.[64,66–68] In those 4 studies, pyelonephritis was described as fever of more than 38°C or 38.5°C and positive urine culture results. In 1 of those studies,[67] dimercaptosuccinic acid scanning results consistent with acute pyelonephritis represented an additional requirement for inclusion. The remaining studies had slightly different inclusion criteria. In the study by Craig et al[71] from 2009, symptoms consistent with UTI and positive urine culture results were required for inclusion. Fever was documented for 79% of enrolled children (454 of 576 children). In the study by Brandström et al,[70] 96% of enrolled children (194 of 203 children) had pyelonephritis, defined in a similar manner as in the 6 initial studies. The remaining patients were enrolled after prenatal diagnosis of VUR. The 2 included abstracts described studies that enrolled any child with VUR and not only children who had had pyelonephritis.[104,105] Seven of the 8 studies (all except the study by Reddy et al[108]) reported a gender ratio. Among those studies, there were 67% girls and 33% boys. Six studies compared antimicrobial treatment with no treatment. Only 2 studies were placebo controlled, and those 2 were the only blinded studies.[69,105] The grade of VUR among the enrolled children varied from 0 to V, but few of the children had grade V VUR.

The ages of children included in the initial meta-analyses were 0 to 18 years; therefore, some children were included who were outside the target

TABLE 10 Studies Included in Meta-analysis

Study	Study Sites	*n*		Age	VUR Grade	Antimicrobial Agents	Control	Follow-up Period, mo	Outcome
		VUR	No VUR						
Craig et al[105] (2002)	Australia	46	0	0–3 mo	I–V	TMP-SMX	Placebo	36	UTI and renal damage
Craig et al[69] (2009)	Australia	243	234	0–18 y	I–V	TMP-SMX	Placebo	12	Symptomatic UTI, febrile UTI, hospitalization, and renal scarring
Garin et al[67] (2006)	Chile, Spain, United States	113	105	3 mo to 18 y	0–III	TMP-SMX/ nitrofurantoin	No treatment	12	Asymptomatic UTI, cystitis, pyelonephritis, and renal scarring
Brandström et al[70] (2010)	Sweden	203	0	1–2 y	III–IV	TMP-SMX/cefadroxil, nitrofurantoin	No treatment	48	Febrile UTI, reflux status, and renal scarring
Montini et al[66] (2008)	Italy	128	210	2 mo to 7 y	0–III	TMP-SMX/amoxicillin-clavulanate	No treatment	12	Febrile UTI and renal scarring
Pennesi et al[68] (2008)	Italy	100	0	0–30 mo	II–IV	TMP-SMX	No treatment	48	UTI and renal scarring
Reddy et al[104] (1997)	United States	29	0	1–10 y	I–V	TMP-SMX/ nitrofurantoin	No treatment	24	UTI, progression of disease, need for surgery, parental compliance
Roussey-Kesler et al[64] (2008)	France	225	0	1–36 m	I–III	TMP-SMX	No treatment	18	Febrile and afebrile UTI

TMP-SMX indicates trimethoprim-sulfamethoxazole.

age range for this report and for whom other factors (eg, voiding and bowel habits) might have played a role. The median age of the included children, however, was not above 3 years in any of the included studies in which it was reported. Separate meta-analyses were subsequently performed for the subgroup of children who were 2 to 24 months of age. The duration of antimicrobial treatment and follow-up monitoring ranged from 12 to 48 months. The antimicrobial agents used were trimethoprim-sulfamethoxazole (1–2 or 5–10 mg/kg),[64,68,69,105] trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid (15 mg/kg),[66] trimethoprim-sulfamethoxazole or nitrofurantoin,[67,104] or trimethoprim-sulfamethoxazole, cefadroxil, or nitrofurantoin.[70] Urine collection methods differed among studies. Bag specimens were reported for 3 studies.[64,66,70] In an additional 4 studies, the description of the urine collection methods did not exclude the use of bag specimens.[67,68,104,105] Recurrent UTI was described as (1) asymptomatic bacteriuria (diagnosed through screening cultures), (2) cystitis, (3) febrile UTI, and (4) pyelonephritis (diagnosed on the basis of focal or diffuse uptake on dimercaptosuccinic acid scans) in the different articles.

Quality Assessment

The included studies received scores (from 2 assessors) from 7 to 26 (scale range: 0–32) with the scoring system described by Downs and Black,[6] with a median score of 16. Score deductions resulted from lack of blinding of patients (all except 2 studies[69,105]), lack of blinding of assessors (all except 2 studies[69,105]), limited or no information about patients lost to follow-up monitoring (3 studies[64,67,104]), lack of reporting of adverse effects (all except 2 studies[66,69]), and small sample sizes. The lowest scores, 7 and 12, were received by the 2 abstracts because of lack of details in the descriptions of the methods.[104,105]

Antimicrobial Therapy Versus No Treatment

Overview of Findings

Described here are the results of several meta-analyses, subdivided according to type of recurrence (pyelonephritis versus UTI), degree of VUR (none to grade V), and patient age. In summary, antimicrobial prophylaxis does not seem to reduce significantly the rates of recurrence of pyelonephritis, regardless of age or degree of reflux. Although prophylaxis seems to reduce significantly but only slightly the risk of UTI when all forms are included, most of this effect is attributable to reductions in rates of cystitis or asymptomatic bacteriuria, which would not be expected to lead to ongoing renal damage.

Recurrence of Pyelonephritis/Febrile UTI Among All Studied Children With VUR of Any Grade

Recurrence of pyelonephritis was reported in 6 of the 8 studies. The study by Pennesi et al[68] presented the results as recurrence of pyelonephritis, but recurrence was defined as episodes of fever *or* "symptoms of UTI." When contacted, this author confirmed that all reported recurrences were characterized by fever above 38.5°C. Therefore, the article was included in the meta-analysis. With a random-effects model, there was no significant difference in rates of recurrence of pyelonephritis for children who received antimicrobial therapy and those who did not. This meta-analysis yielded a RR of 0.77 (95% CI: 0.47–1.24) (Fig 8). Heterogeneity test-

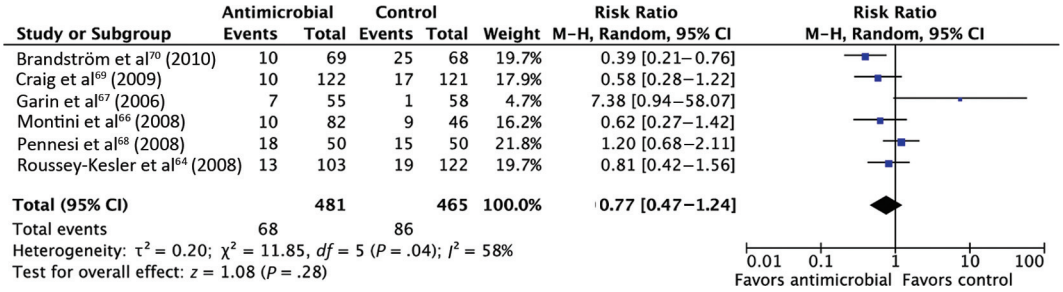

FIGURE 8

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children with VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

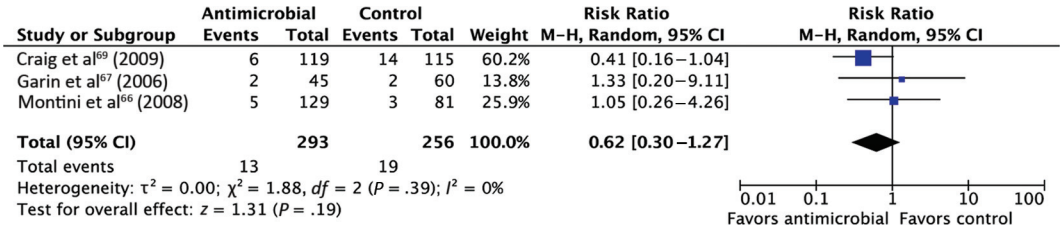

FIGURE 9

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children without VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

ing results were significant ($P = .04$), which indicated statistical heterogeneity between studies.

Recurrence of Pyelonephritis/Febrile UTI Among Children of All Ages Without VUR

There was no significant difference in rates of recurrence of pyelonephritis for children without VUR who received antimicrobial therapy and those who did not. With random-effects modeling, the meta-analysis yielded a RR of 0.62 (95% CI: 0.30–1.27) (Fig 9). Heterogeneity testing results were not significant ($P = .39$). Because no difference was detected with a random-effects model and there was no statistical heterogeneity in this analysis, analysis also was conducted with a fixed-effects model. With fixed-effects modeling, the meta-analysis yielded a RR of 0.61 (95% CI: 0.31–1.23).

Recurrence of Pyelonephritis/Febrile UTI Among Children of All Ages With VUR, According to Grade

Table 11 summarizes the results of separate meta-analyses of subpopulations from each study with different grades of VUR. None of those analyses showed a statistically significant difference in rates of recurrence with random- or fixed-effects modeling. Random-effects modeling results are presented.

TABLE 11 Combined Estimates of Effect of Antimicrobial Prophylaxis on Prevention of Pyelonephritis for All Children According to Grade of VUR

VUR Grade	No. of Children	No. of Studies	RR (95% CI)[a]
0	549	3	0.62 (0.30–1.27)
I–II	455	5	0.94 (0.49–1.80)
III	347	6	0.74 (0.42–1.29)
IV	122	3	0.69 (0.39–1.20)
V	5	1	0.40 (0.08–1.90)

[a] From random-effects model.

Recurrence of Pyelonephritis/Febrile UTI Among Children 2 to 24 Months of Age With VUR of Any Grade

There was no significant difference in rates of recurrence of pyelonephritis for children 2 to 24 months of age with VUR who received antimicrobial agents and those who did not. With random-effects modeling, the meta-analysis yielded a RR of 0.78 (95% CI: 0.48–1.26) (Fig 10). Heterogeneity testing results were not significant ($P = .07$). With fixed-effects modeling, the meta-analysis yielded a RR of 0.79 (95% CI: 0.58–1.07). Heterogeneity testing results were not significant ($P = .07$).

Recurrence of Pyelonephritis/Febrile UTI Among Children 2 to 24 Months of Age With No VUR

There was no significant difference in rates of recurrence of pyelonephritis for children 2 to 24 months of age without VUR who received antimicrobial agents and those who did not. With random-effects modeling, the meta-analysis yielded a RR of 0.55 (95% CI:

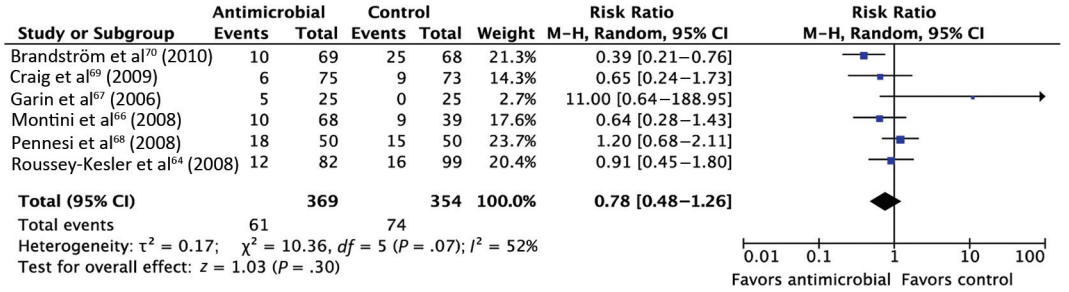

FIGURE 10

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age with any grade of VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

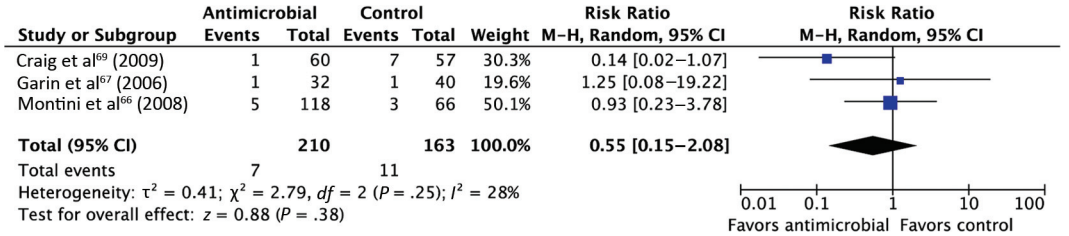

FIGURE 11

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age without VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

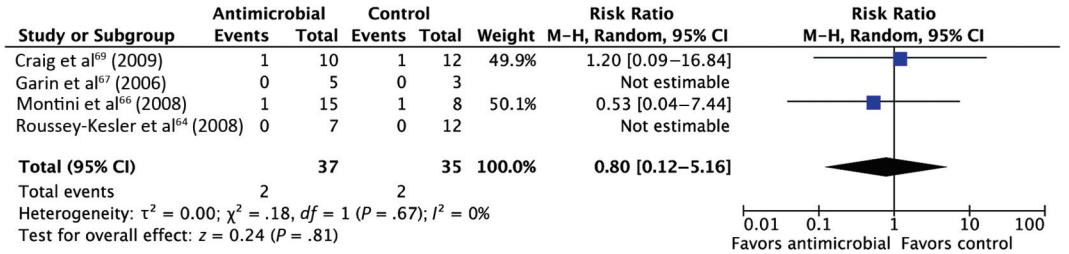

FIGURE 12

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age with grade I VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

0.15–2.08) (Fig 11). Heterogeneity testing results were not significant ($P = .25$). With fixed-effects modeling, the meta-analysis yielded a RR of 0.48 (95% CI: 0.18–1.27). Heterogeneity testing results were not significant ($P = .25$).

Recurrence of Pyelonephritis/Febrile UTI Among Children 2 to 24 Months of Age According to Grade of VUR

When results were analyzed according to VUR grade, there was no significant difference in rates of recurrence of pyelonephritis for children 2 to 24 months of age who received antimicrobial agents and those who did not in any of the analyses, with random- or fixed-effects modeling. Results of random-effects modeling are presented in Figs 12 through 16. Heterogeneity testing results were not significant in any of the analyses.

Recurrence of Any Type of UTI Among Children of All Ages With VUR of Any Grade

In this meta-analysis, in which the 2 published abstracts that never resulted in published articles were included, there was a statistically significant difference in rates of recurrence of any type of UTI for children with VUR who received antimicrobial agents and those who did not. With random-effects modeling, the meta-analysis yielded a RR of 0.70 (95% CI: 0.51–0.96) (Fig 17). Heterogeneity testing results were not significant ($P = .20$).

The inclusion of the published abstracts[104,105] in these meta-analyses can be criticized, because the investigators in those studies enrolled all children with VUR and not just those who had been diagnosed as having UTI; therefore, *recurrent* UTIs were not measured. With exclusion of the 2 abstracts from the meta-analyses for prevention of any UTI, the RR with random-effects modeling would be 0.73 (95% CI: 0.53–1.01). Heterogeneity testing results were not significant ($P = .16$).

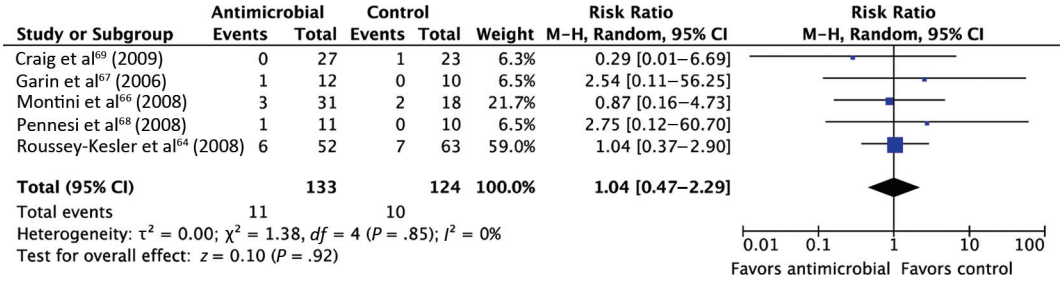

FIGURE 13

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age with grade II VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

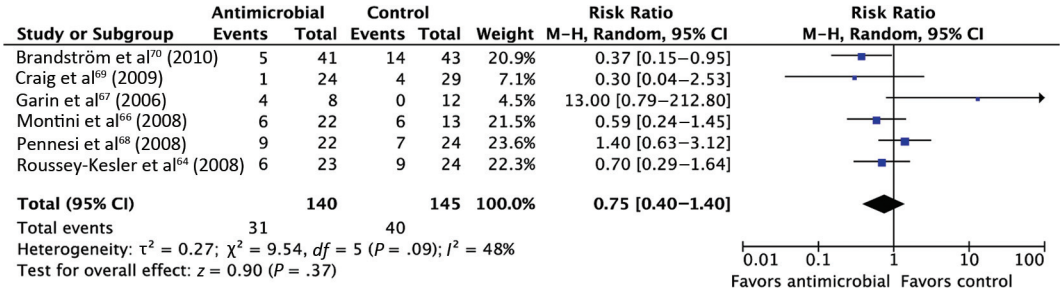

FIGURE 14

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age with grade III VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

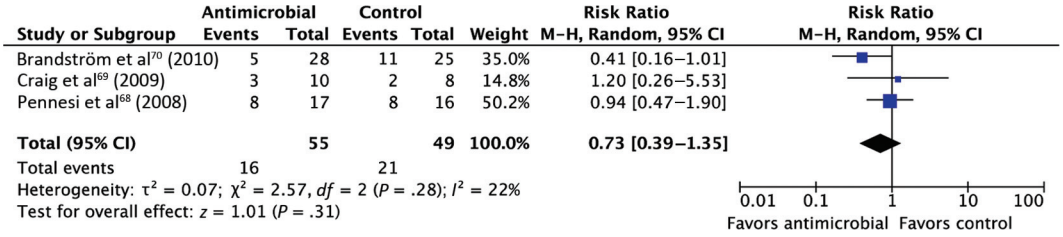

FIGURE 15

Combined estimates of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age with grade IV VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

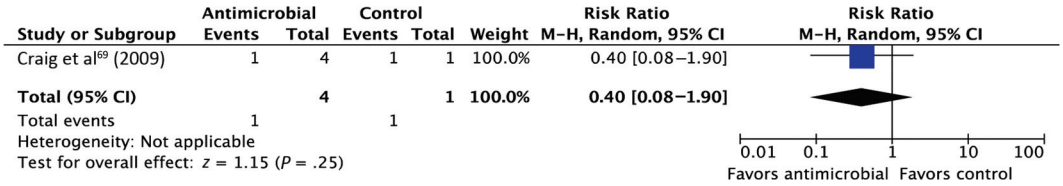

FIGURE 16

Estimate of the effect of antimicrobial prophylaxis on prevention of pyelonephritis in children 2 to 24 months of age with grade V VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

Recurrence of Any Type of UTI Among Children of All Ages Without VUR

There was no significant difference in rates of recurrence of any type of UTI for children without VUR who received antimicrobial agents and those who did not. With random-effects modeling, the meta-analysis yielded a RR of 0.72 (95% CI: 0.43–1.20) (Fig 18). Heterogeneity testing results were not significant ($P = .37$).

Effect on Studies of Inclusion of Bag Specimens

With the exception of the study by Craig et al,[69] no studies reported that bag urine specimens were excluded. The inclusion of such specimens might

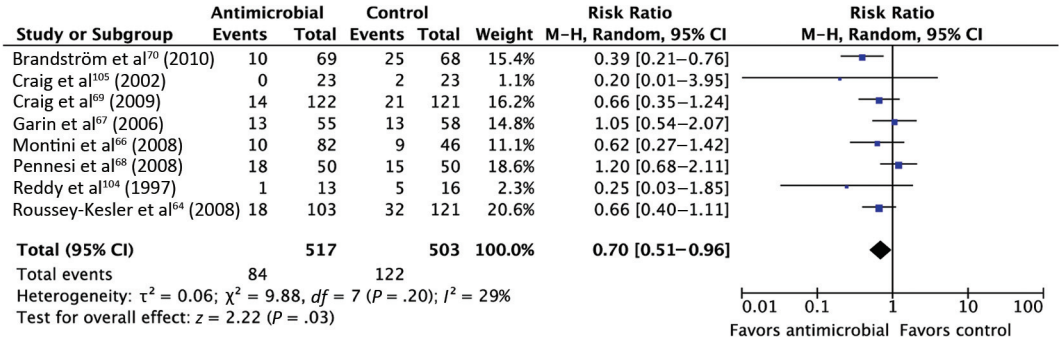

FIGURE 17

Combined estimates of the effect of antimicrobial prophylaxis on prevention of any UTI in children with any grade of VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

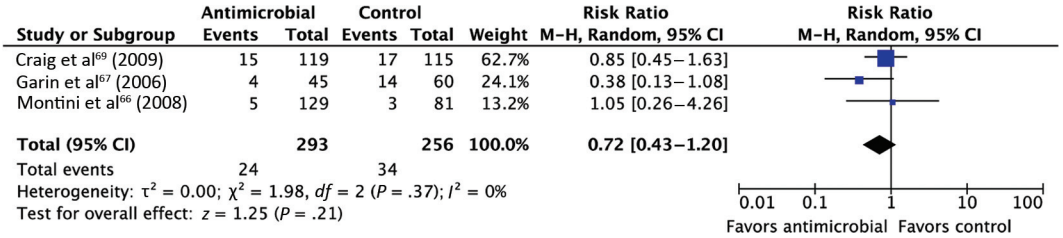

FIGURE 18

Combined estimates of the effect of antimicrobial prophylaxis on prevention of any UTI in children without VUR, from random-effects modeling. RRs and 95% CIs are shown. M-H indicates Mantel-Haenszel.

have resulted in increased numbers of false-positive urine culture results in both the antimicrobial prophylaxis and control groups, yielding a bias toward the null hypothesis in those studies.

Results of Excluded Study

The study by Lee et al[65] was excluded from the meta-analysis because it compared antimicrobial prophylaxis with probiotic treatment. A total of 120 children 13 to 36 months of age with a history of UTI and VUR of grade I to V who had been receiving trimethoprim-sulfamethoxazole once daily for 1 year were again assessed for VUR; if VUR persisted, then children were assigned randomly either to continue to receive trimethoprim-sulfamethoxazole or to receive *Lactobacillus acidophilus* twice daily for 1 additional year. The study showed no statistical difference in recurrent UTI rates between the 2 groups during the second year of follow-up monitoring.

Antimicrobial Prophylaxis and Antimicrobial Resistance

The antimicrobial resistance patterns of the pathogens isolated during UTI recurrences were assessed in 5 of the RCTs included in the meta-analyses.[64,66,68–70] All authors concluded that UTI recurrences with antimicrobial-resistant bacteria were more common in the groups of children assigned randomly to receive antimicrobial prophylaxis. In the placebo/surveillance groups, the proportions of resistant bacteria ranged from 0% to 39%; in the antimicrobial prophylaxis groups, the proportions of resistant bacteria ranged from 53% to 100%. These results are supported by other studies in which antimicrobial prophylaxis has been shown to promote resistant organisms.[106,107]

Surgical Intervention Versus Antimicrobial Prophylaxis

Data on the effectiveness of surgical interventions for VUR are quite limited. To date, only 1 RCT has compared surgical intervention (only endoscopic therapy) for VUR with placebo treatment.[70] In that study, there was a statistically significant difference in the rates of recurrence of febrile UTI for girls treated with endoscopic therapy and those under surveillance (10 of 43 vs 24 of 42 girls; $P = .0014$). No such difference was noted among boys, for whom the results trended in the opposite direction (4 of 23 vs 1 of 26 boys). A meta-analysis examined the outcomes of UTIs and febrile UTIs in children assigned randomly to either reflux correction plus antimicrobial therapy or antimicrobial therapy alone.[108] By 2 years, the authors found no significant reduction in the risk of UTI in the surgery plus antimicrobial therapy group, compared with the antimicrobial therapy-only group (4 studies; RR: 1.07 [95% CI: 0.55–2.09]). The frequency of febrile UTIs was reported in only 2 studies. Children in the surgery plus

antimicrobial therapy group had significantly fewer febrile UTIs than did children in the antimicrobial therapy-only group between 0 and 5 years after intervention (RR: 0.43 [95% CI: 0.27–0.70]). Although there may be some promise in endoscopic interventions for children with VUR, to date there are insufficient data to show whether and for whom such interventions may be helpful.

Long-term Consequences of VUR

The link between VUR discovered after the first UTI and subsequent hypertension and end-stage renal disease remains tenuous at best. There have been no longitudinal studies monitoring children long enough to quantify these outcomes. Retrospective studies evaluated highly selected populations, and their findings might not apply to otherwise healthy children with a first UTI.[109–112] Ecologic data from Australia demonstrated no changes in the rates of hypertension and renal failure since the widespread introduction of antimicrobial prophylaxis and ureteric reimplantation surgery for VUR in the 1960s.[113]

DISCUSSION

Review of the evidence regarding diagnosis and management of UTIs in 2- to 24-month-old children yields the following. First, the prevalence of UTI in febrile infants remains about the same, at ~5%. Studies have provided demographic features (age, race, and gender) and clinical characteristics (height and duration of fever, other causes of fever, and circumcision) that can help clinicians identify febrile infants whose low risk of UTI obviates the need for further evaluation.

Among children who do not receive immediate antimicrobial therapy, UTI can be ruled out on the basis of completely negative urinalysis results. For this purpose, enhanced urinalysis is preferable. However, facilities for urine microscopy with counting chambers and Gram staining may not be available in all settings. A urine reagent strip with negative nitrite and leukocyte esterase reaction results is sufficient to rule out UTI if the pretest risk is moderate (~5%). Diagnosis of UTI is best achieved with a combination of culture and urinalysis. Cultures of urine collected through catheterization, compared with SPA, are nearly as sensitive and specific but have higher success rates and the process is less painful. Cultures of urine collected in bags have unacceptably high false-positive rates.

The previous guideline recommended VCUG after the first UTI for children between 2 and 24 months of age. The rationale for this recommendation was that antimicrobial prophylaxis among children with VUR could reduce subsequent episodes of pyelonephritis and additional renal scarring. However, evidence does not support antimicrobial prophylaxis to prevent UTI when VUR is found through VCUG. The only statistically significant effect of antimicrobial prophylaxis was in preventing UTI that included cystitis and asymptomatic bacteriuria. Statistically significant differences in the rates of febrile UTI or pyelonephritis were not seen. Moreover, VCUG is one of the most uncomfortable radiologic procedures performed with children.[114–116]

Even if additional studies were to show a statistically significant effect of prophylaxis in preventing pyelonephritis, our point estimates suggest that the RR would be ~0.80, corresponding to a reduction in RR of 20%. If we take into account the prevalence of VUR, the risk of recurrent UTI in those children, and this modest *potential* effect, we can determine that ~100 children would need to undergo VCUG for prevention of 1 UTI in the first year. Even more striking is the fact that the evidence of benefit is the same (or better) for children with *no* VUR, which makes the benefit of VCUG more dubious. Taken in light of the marginal cost-effectiveness of the procedure found under the more-optimistic assumptions in the 1999 technical report, these data argue against VCUG after the first UTI. VCUG after a second or third UTI would have a higher yield of higher grades of reflux, but the optimal care for infants with higher-grade reflux is still not clear. Ultrasonography of the kidneys, ureters, and bladder after a first UTI has poor sensitivity and only a modest yield of "actionable" findings. However, the procedure is less invasive, less uncomfortable, and less risky (in terms of radiation) than is VCUG.

There is a significant risk of renal scarring among children with febrile UTI, and some evidence suggests that early antimicrobial treatment mitigates that risk. It seems prudent to recommend early evaluation (in the 24- to 48-hour time frame) of subsequent fevers and prompt treatment of UTI to minimize subsequent renal scarring.

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OVERSIGHT BY THE STEERING COMMITTEE ON QUALITY IMPROVEMENT AND MANAGEMENT, 2009–2011

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ACKNOWLEDGMENTS

The committee gratefully acknowledges the generosity of the researchers who graciously shared their data to permit the data set with data for 1096 infants 2 to 24 months of age according to grade of VUR to be compiled, that is, Drs Per Brandström, Jonathan Craig, Eduardo Garin, Giovanni Montini, Marco Pennesi, and Gwenaelle Roussey-Kesler.

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Pediatrics 2011;128;e749; originally published online August 28, 2011;
DOI: 10.1542/peds.2011-1332