Antibiotic Prophylaxis for Urinary Tract Infection–Related Renal Scarring: A Systematic Review

Ian K. Hewitt, MB, BS,[a] Marco Pennesi, MD,[b] William Morello, MD,[c] Luca Ronfani, MD,[d] Giovanni Montini, MD[c]

abstract

CONTEXT: Acute pyelonephritis may result in renal scarring. Recent prospective studies have shown a small benefit of antibiotic prophylaxis in preventing symptomatic and febrile urinary tract infections (UTIs), while being underpowered to detect any influence in prevention of renal damage.

OBJECTIVES: Review of the literature and a meta-analysis to evaluate the effect of antibiotic prophylaxis on UTI-related renal scarring.

DATA SOURCES: Medline, Embase, and Cochrane Controlled Trials Register electronic databases were searched for studies published in any language and bibliographies of identified prospective randomized controlled trials (RCTs) performed and published between 1946 and August 2016.

STUDY SELECTION: Subjects 18 years of age or younger with symptomatic or febrile UTIs, enrolled in prospective RCTs of antibiotic prophylaxis where ^{99m}Tc dimercaptosuccinic acid scans were performed at entry into the study and at late follow-up to detect new scar formation.

DATA EXTRACTION: The literature search, study characteristics, inclusion and exclusion criteria, and risk of bias assessment were independently evaluated by 2 authors.

RESULTS: Seven RCTs (1427 subjects) were included in the meta-analysis. Our results show no influence of antibiotic prophylaxis in preventing renal scarring (pooled risk ratio, 0.83; 95% confidence interval, 0.55–1.26) as did a subanalysis restricted to those subjects with vesicoureteral reflux (pooled risk ratio, 0.79; 95% confidence interval, 0.51–1.24).

LIMITATIONS: Limitations include the small number of studies, short duration of follow-up, and insufficient children with high-grade dilating reflux and/or renal dysplasia enrolled in the studies.

CONCLUSIONS: Antibiotic prophylaxis is not indicated for the prevention of renal scarring after a first or second symptomatic or febrile UTI in otherwise healthy children.

[a]*Department of Paediatric Nephrology, Princess Margaret Hospital for Children, Perth, Western Australia, Australia;* [b]*Department of Pediatrics and* [d]*Epidemiology and Biostatistics Unit, Institute for Maternal and Child Health – IRCCS "Burlo Garofolo," Trieste, Italy; and* [c]*Pediatric Nephrology, Dialysis and Transplant Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, University of Milan, Italy*

Dr Hewitt conceptualized the paper, selected the studies and performed the meta-analysis, and drafted the initial manuscript; Dr Pennesi conceived the meta-analysis, selected the studies for review, and assisted with the meta-analysis; Dr Morello participated in the selection of the studies and drafting of the manuscript; Dr Ronfani conceived the meta-analysis and reviewed the statistical analyses; Prof Montini conceptualized the paper, selected the studies for the meta-analysis, drafted the initial manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Febrile urinary tract infection (UTI) is a common bacterial infection in young children,[1] with ~19% having evidence of renal scarring on a late follow-up ^{99m}Tc dimercaptosuccinic acid (DMSA) scan.[2] Although the prognosis of a single episode of febrile UTI is usually good, major concerns are related to the possible long-term effects on renal function, secondary to the appearance of renal scarring.

Long-term antibiotic prophylaxis has been advocated to reduce the incidence of UTI with the intent to reduce related renal scarring; however, it is not without costs and risks. The purpose of this systematic review is to determine whether those costs and risks might be outweighed by a benefit of reducing permanent renal damage in the form of pyelonephritic scarring. We are not of the view that the prevention of a single symptomatic or febrile UTI in the absence of a significant reduction in scarring warrants up to 16 patient-years of continuous antibiotic prophylaxis,[3] along with reconsideration of the need for invasive radiologic investigation to determine whether vesicoureteral reflux (VUR) has resolved.[4]

The majority of the published studies on antibiotic prophylaxis have focused on the reduction in the number of UTIs, although the most appropriate surrogate end point to evaluate the long-term efficacy, in terms of renal function, is the prevention of postinfectious renal scars, which represent the most important adverse outcome from the patient's perspective.

Hence, we have undertaken a systematic review of the literature and a meta-analysis to explore the role of antibiotic prophylaxis as a preventive measure in the appearance and worsening of renal scars in children after a symptomatic or febrile UTI, given that no single study to date has been sufficiently powered to detect differences in the rates of scarring as a primary outcome.

METHODS

The meta-analysis was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[5]; however, it was not registered on a Web site. Searches were conducted in Medline (1946 to August 2016), Embase (1980 to August 2016), and the Cochrane Controlled Trials Register for studies reporting on UTIs, with reports limited to children (≤18 years of age) who had been randomized in a study involving the use of prophylactic antibiotics. The children needed to be prospectively randomized to a treatment (antibiotic prophylaxis) group or control (no treatment or placebo) group. The search terms used are included in the Supplemental Information. The electronic search was supplemented by a search of the bibliographies of the included articles. A requirement for the detection of renal scarring was the need for a technetium DMSA scan at entry into the study with a late scan 12 months to 2 years later to document any scarring. The reporting of DMSA scans in the studies was extracted manually because they were not reliably documented in the Medical Subject Headings of the references retrieved electronically.

The DMSA scan at entry was necessary for the detection of renal parenchymal involvement of the UTI with a photon-deficient area, or previous scarring where, in addition to a photon-deficient area, contraction and distortion of the renal cortex with loss of volume is often seen. The late DMSA scan was necessary to detect new scarring and determine whether the intervention (antibiotic prophylaxis) led to a reduction in renal parenchymal damage. The search was conducted without exclusion based on language of publication.

The study selection was performed by 2 independent reviewers (I.K.H. and M.P.) based on titles and abstracts. The full text of the papers that appeared to meet the selection criteria were reviewed. Disagreement in selection and full-text review was resolved by consensus. The review outcome was the presence of new scar formation or worsening of existing scars as determined by DMSA.

Statistical Methods

A Mantel-Haenszel fixed-effects meta-analysis was performed, combining data across studies to test the efficacy of the intervention (continuous antibiotic prophylaxis) versus controls (placebo or no treatment) on the risk of new scars or worsening of existing scars. Descriptive statistical analyses were undertaken by using risk ratios (RR) and 95% confidence intervals (CIs) as appropriate. Heterogeneity across the included studies was evaluated. A subgroup analysis was performed that was restricted to those children with VUR. The statistics were performed with Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

Risk of Bias

The bias assessment was conducted independently by 2 study authors (I.K.H., M.P.) in accordance with the Cochrane Collaborative checklist.[6] Differences were resolved by discussion. Funnel plots were used to detect evidence of publication bias. A subgroup analysis was undertaken for those children with VUR, with the bias assessment repeated.

RESULTS

Search Results

A total of 1398 studies were identified by using the search

criteria listed in the Supplemental Information. After electronic removal of duplicates and screening of titles and abstracts, 189 potentially relevant studies were identified for full review. A detailed analysis of these studies, including a full-text review when an article might meet selection criteria, was undertaken. Studies published in languages other than English were translated by study authors fluent in the language, and recourse to institutional translation staff proved unnecessary. The search performed in the www.clinicaltrial.gov database (26 studies identified) did not find any additional randomized controlled trials (RCTs). Seven published studies fulfilled all criteria for inclusion in the meta-analysis and were selected for the final review (Fig 1).

Description of Excluded Studies

The broad search terms were designed to capture all possible relevant studies. The most common papers excluded were comments and reviews that contained the search terms, duplicate articles reporting on different aspects of the same studies, studies of agents other than antibiotics, adult studies, and prospective studies often comparing different antibiotics or antibiotics versus surgical intervention without a control placebo or no treatment group. Three studies addressed antenatal hydronephrosis without a preceding UTI. One study was reported in abstract form at a meeting as having been initiated; however, a search of the authors and title failed to disclose any published outcomes.

Description of Included Studies

All the studies included in this meta-analysis were prospective RCTs. Seven RCTs[3,7–12] (1427 subjects) were included in the meta-analysis on the effect of antibiotic prophylaxis on UTI-related renal scarring. A subgroup meta-analysis was conducted on the included trials, restricting the population to those with documented VUR (1076 subjects) to determine whether prophylaxis proved to be of benefit in this population at increased risk of UTI. Table 1 summarizes the characteristics of the included studies.

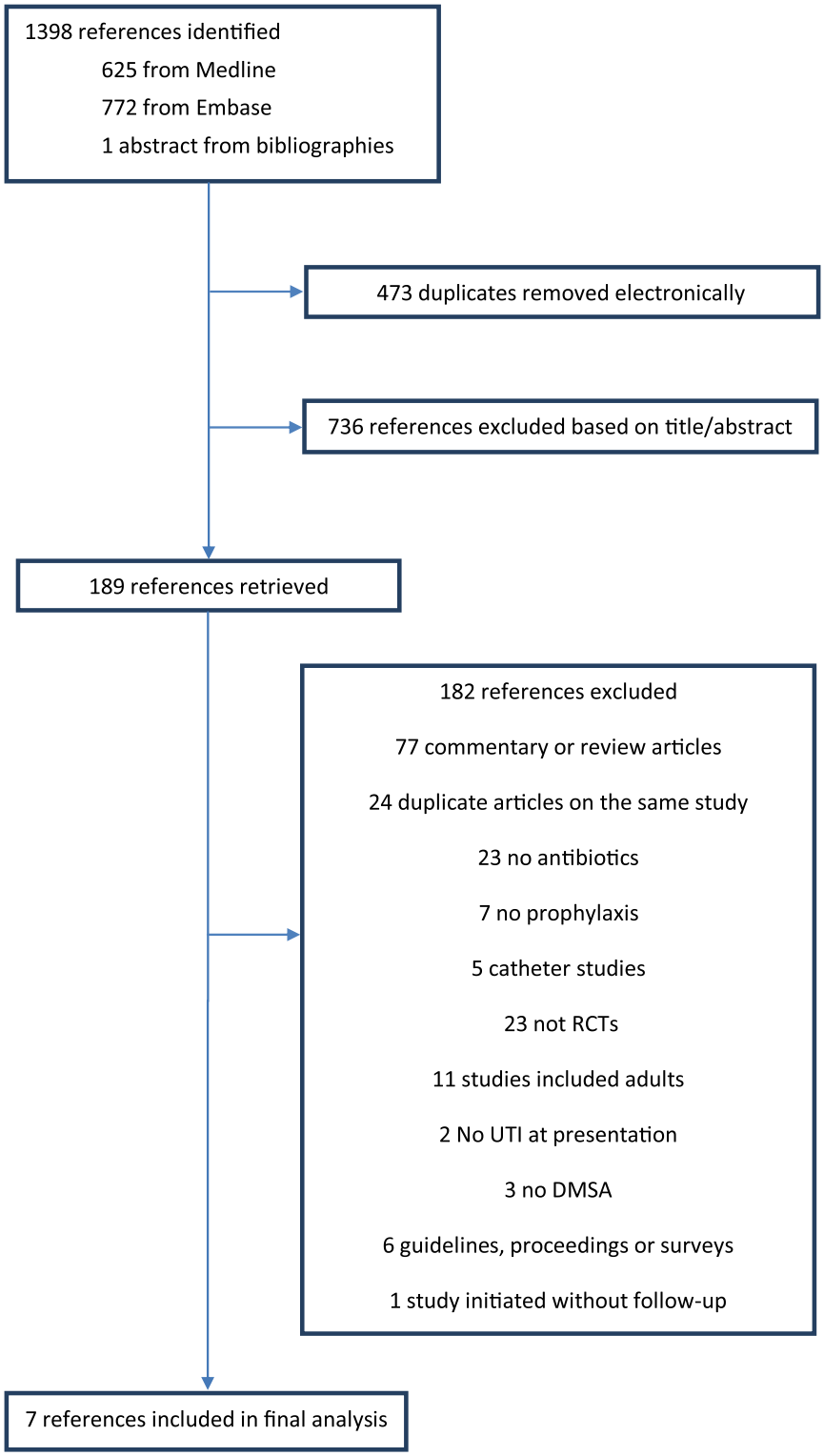

FIGURE 1
Flow diagram of selection process for the systematic review.

TABLE 1 Characteristics of the Included Studies

	Garin et al, 2006[7]	Pennesi et al, 2008[9]	Montini et al, 2008[8]	Craig et al, 2009[10]	Brandström et al, 2011[11]	Hoberman, et al 2014[3]	Hari et al, 2015[12]
Total enrolled patients	218	100	338	576	203	607	93
No. of patients with a complete DMSA evaluation	218	100	295	151	136	447	80
Boy/girl	40/178	52/48	104/234	207/369	75/128	49/558	62/31
Age, y	≤18	≤2.5	≤7	≤18	≤2	≤6	≤12
VUR grade	0–III	II–IV	0–III	0–V	III–IV	I–IV	I–IV
Previous UTI	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design	Open-label	Open-label	Open-label	Placebo	Open-label	Placebo	Placebo
Type of prophylaxis	TMP/SMZ	TMP/SMZ	TMP/SMZ or Amoxiclavulanate	TMP/SMZ	Trimethoprim	TMP/SMZ	TMP/SMZ
Timing of follow-up DMSA, y	1	2	1	1	2	1 and 2	1

TMP/SMZ, Trimethoprim/Sulfamethoxazole.

Risk of Bias in the Included Studies

The risk of bias graph (Fig 2) demonstrates the major bias to be a lack of adequate blinding. Four studies[7–9,11] provided no treatment in the control arm, whereas only 3 studies[3,10,12] provided a placebo. For all studies selected, scarring was a secondary outcome. The primary outcome was always symptomatic or febrile UTI recurrence. One study[10] left the performance and timing of DMSA scans for the detection of scarring to the discretion of the treating physician, introducing a bias in terms of those selected for investigation of scarring. In several studies, the method of random sequence generation or the method of allocation concealment was not clearly identified.[7,11] In 1 study, attrition and reporting bias were possible.[7] None of the studies reported a loss to follow-up of >10% in either arm.

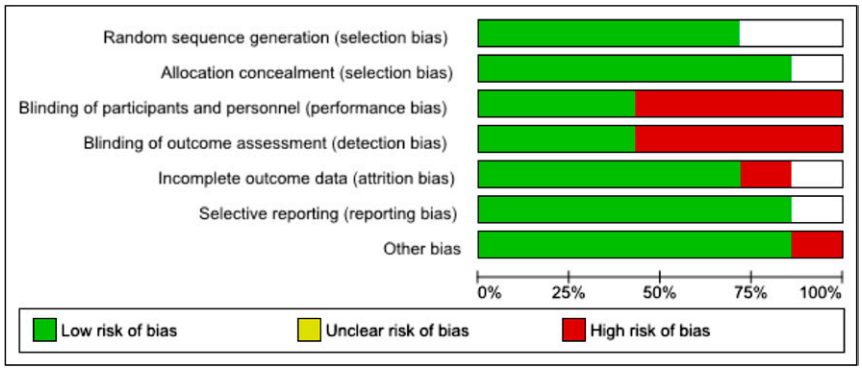

FIGURE 2
Risk of bias graph.

Efficacy of Interventions

Seven RCTs[3,7–12] (1427 subjects) were included in the meta-analysis, with 6 RCTs[3,7–9,11,12] (1004 subjects) included in the subgroup meta-analysis restricted to those with VUR. Both meta-analyses did not show differences in the incidence of scarring between the prophylaxis and no prophylaxis groups (pooled RR, 0.83; 95% CI, 0.55–1.26 [renal scarring in all subjects]; RR, 0.82; 95% CI 0.51–1.31 [renal scarring restricted to subjects with VUR]) (Figs 3 and 4). New scarring was shown in 5.7% of all children and in 6.3% of those with VUR. There was no significant heterogeneity. The funnel plots did not demonstrate evidence of publication bias (Figs 5 and 6).

DISCUSSION

The attention of pediatricians and researchers investigating UTIs as a risk factor for renal damage has focused on the risk of UTI recurrence, rather than the risk of scarring, as a surrogate end point for long-term renal function. In this respect, almost all of the RCTs performed involving antibiotic prophylaxis have assumed that a reduction in recurrent infection rates would result in a significant reduction of scarring. Up until now, all trials have failed to demonstrate any benefit with regard to the reduction of UTI-related renal scarring, apart from the Swedish reflux trial.[11] In this trial of children with dilating VUR, the girls in the control surveillance group compared with the antibiotic prophylaxis group demonstrated a significant increase in new renal damage. Because no single RCT to date has been primarily designed or powered to investigate the

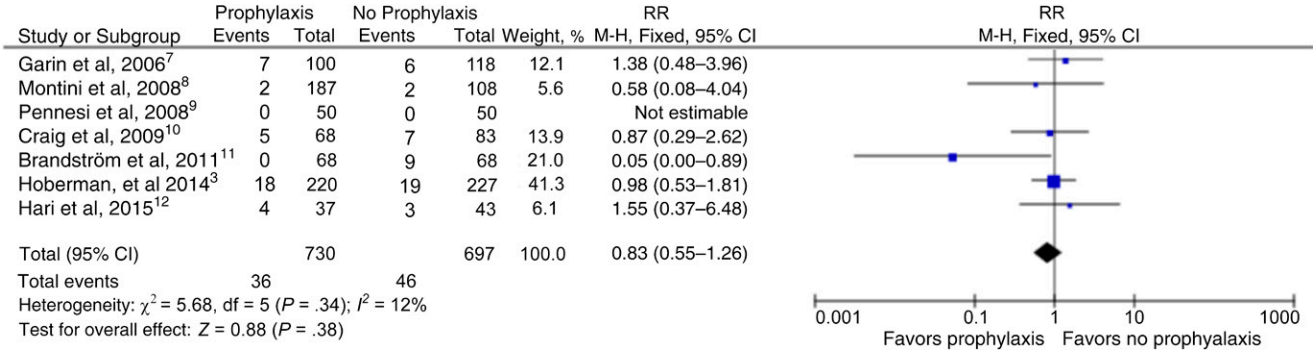

FIGURE 3
Risk of renal damage (scarring) according to the use or absence of antibiotic prophylaxis. df, degrees of freedom; M-H, Mantel-Haenszel.

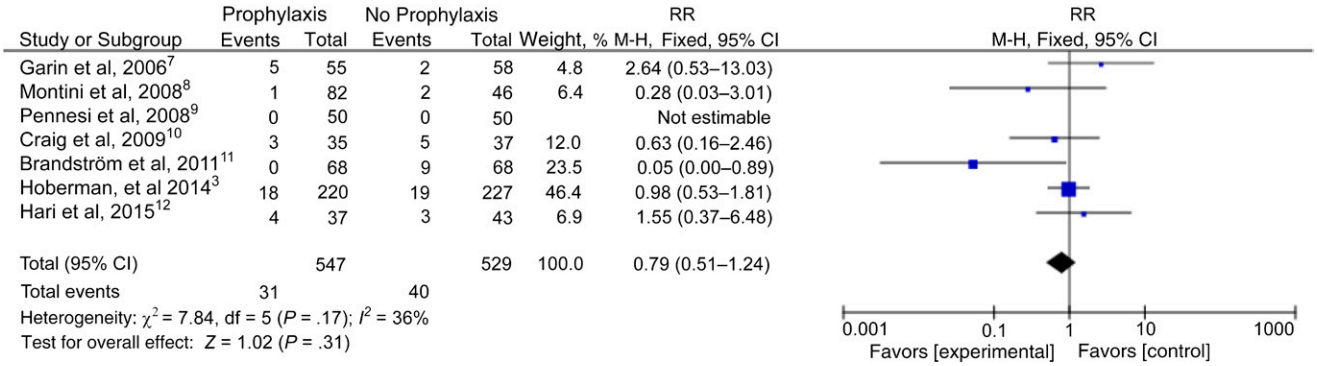

FIGURE 4
Risk of renal damage (scarring) according to the use or absence of antibiotic prophylaxis restricted to children with VUR. df, degrees of freedom; M-H, Mantel-Haenszel.

risk of scarring, we performed a systematic review and a meta-analysis to additionally explore the possible influence of antibiotic prophylaxis on scarring. In the >1400 children (mostly girls) studied who presented with febrile or symptomatic UTI, there was no significant influence of antibiotic prophylaxis in the prevention of scarring, as demonstrated by the meta-analysis. The same holds true for the subgroup analysis restricted to the 1076 children with VUR. Furthermore, the risk of developing new scarring was low, ~6%, in the population considered, with the great majority of kidneys evaluated being normal at presentation and at the end of follow-up. This indicates that the majority of children with a symptomatic or first

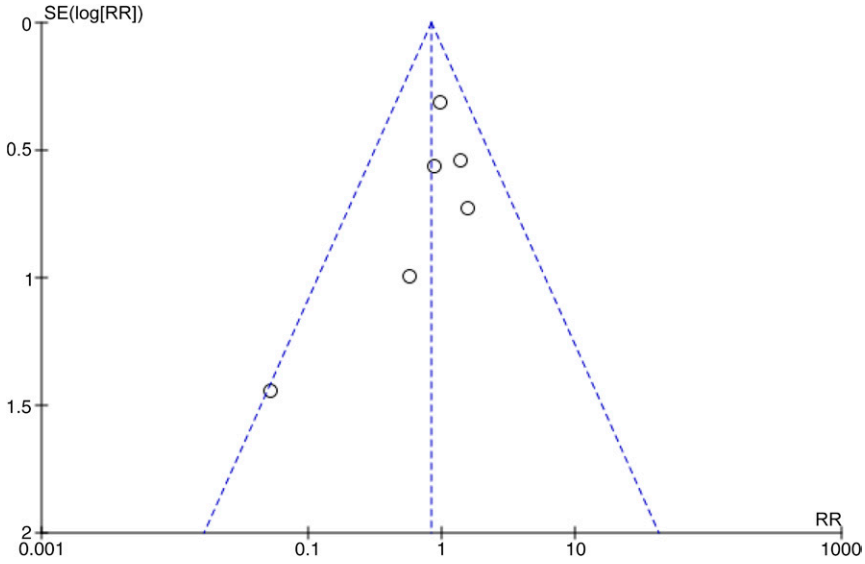

FIGURE 5
Funnel plot for all included studies of scarring.

febrile UTI have normal kidneys (as exemplified by the Randomized Intervention for Children with Vesicoureteral Reflux study,[3] where 96.4% of 582 children had normal kidneys at enrollment) and are not at risk for long-term adverse outcomes.

The reduction in febrile UTIs has been minimal, with the largest study[3] requiring 16 or 22 patient-years of antibiotics to prevent 1 symptomatic or 1 febrile UTI, respectively. Given that 19% of febrile UTIs result in scarring,[2] any clinical benefit of prophylaxis is negligible. This lack of influence on scarring is also confirmed by our meta-analysis, which did not demonstrate any benefit, despite the combined studies documenting 1068 patient-years of antibiotic prophylaxis.

Furthermore, the results of these meta-analyses sustain the current watchful-waiting approach of published guidelines for the investigation and management of first febrile UTIs in infants and young children.[13–17] They do not advocate routine antibiotic prophylaxis (Table 2). The American Academy of Pediatrics, in particular, reconsidered its UTI guidelines in light of the Randomized Intervention for Children with Vesicoureteral Reflux trial, the most comprehensive study on this topic, and reaffirmed the 2011 recommendations.[18]

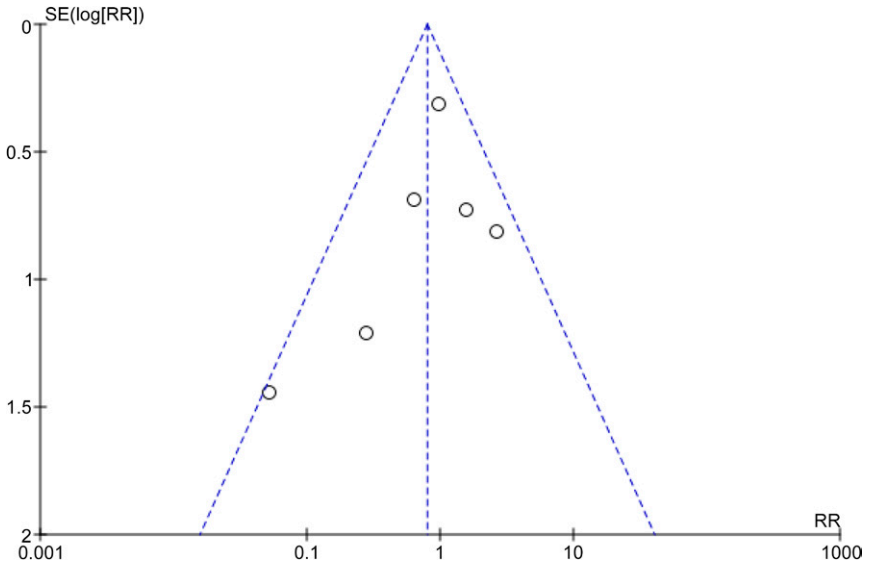

FIGURE 6
Funnel plot for studies of scarring where VUR is present.

Data from the international registries of end-stage renal disease (ESRD)[19–22] show that the population at serious risk of chronic kidney damage are those children, predominantly boys, with significant congenital abnormalities of the kidney and urinary tract (CAKUT), particularly hypodysplasia, whereas the risk of ESRD after UTIs in otherwise healthy children remains anecdotal. CAKUT are the primary cause of ESRD and renal replacement therapy (dialysis or transplantation) in children,[22] and are now detected on antenatal ultrasound. Unfortunately, to the best of our knowledge, no prospective randomized studies have been conducted on this specific population. The rate at which hypodysplastic kidneys decline in function is acknowledged to be slow[20,22]; interventions that might retard the progression of chronic kidney disease in this population of children, including antibiotic prophylaxis, have not been prospectively evaluated. In addition, much needs to be understood regarding the genetic determinants of CAKUT, in particular hypodysplasia and the propensity for scarring.

The limitations of this meta-analysis relate to scarring being a secondary rather than primary outcome in all studies, the absence of blinding and placebo in most studies, the age range of the populations studied

TABLE 2 Investigation and Management of a First Febrile UTI in Children Aged 2 to 24 Months: Published Nephrology Society Guidelines

Guideline	Ultrasound	VCUG	DMSA	Prophylaxis
National Institute for Health and Care Excellence (2007)[13]	Atypical, <6 mo of age	No, unless <6 mo of age with positive US or atypical UTI	Yes >6 mo post-UTI	No
American Academy of Pediatrics (2011)[16]	Yes	No, unless abnormal US	No	No
Italian Society of Pediatric Nephrology (2012)[15]	Yes	No, unless abnormal US or risk factors	Yes >6 mo post-UTI if abnormal US or VUR	No
Kidney Health Australia – Caring for Australasians with Renal Impairment (2014)[14]	Yes, if: no second or third trimester US; <3 mo of age; or atypical UTI	No, unless abnormal US	No	No
Canadian Paediatric Society (2014)[17]	Yes	No, unless abnormal US	No	No

US, ultrasound; VCUG, Voiding Cystourethrogram

varying considerably, and a disproportionate proportion of girls in several studies. The strengths of this meta-analysis relate to the search being restricted to prospective RCTs with a well-defined objective outcome: renal scarring.

This is an exciting and challenging time where it is no longer necessary, nor is it justified, to overinvestigate and treat the vast majority of otherwise healthy children who have an uncomplicated UTI, but rather to focus on those infants and children who are destined to experience chronic kidney disease to determine by what means we can alleviate their suffering. In children with or without VUR and normal kidneys, the absence of any statistical benefit in the reduction of kidney scarring do not justify the possible side effects of long-term antibiotic exposure.

ABBREVIATIONS

CAKUT: congenital abnormalities of the kidney and urinary tract
CI: confidence interval
DMSA: ^{99m}Tc dimercaptosuccinic acid
ESRD: end-stage renal disease
RCT: randomized controlled trial
RR: risk ratio
UTI: urinary tract infection
VUR: vesicoureteral reflux

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Address correspondence to Giovanni Montini, MD, Pediatric Nephrology, Dialysis and Transplant Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, University of Milan, Via della Commenda 9, 20122 Milan, Italy. E-mail: giovanni.montini@unimi.it

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