

Do Various Treatment Modalities of Vesicoureteral Reflux Have Any Adverse Effects in Pediatric Patients? A Meta-Analysis

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Keywords

Vesicoureteral reflux · Urinary tract infections · Renal scar · Meta-analysis

Abstract

Purpose: Vesicoureteral reflux (VUR) is a risk factor for various renal problems like recurrent urinary tract infections (UTIs), pyelonephritis, renal scarring, hypertension, and other renal parenchymal defects. The interventions followed by pediatricians include low-dose antibiotic treatment, surgical correction, and endoscopy. This meta-analysis aimed to assess the advantages and drawbacks of various primary VUR treatment options. **Search Strategy:** The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, reference lists of journals, and abstracts from conference proceedings were all used to find randomized controlled trials. The articles were retrieved from 1985 till 2020. Twenty articles were used for the data analysis. **Criteria for Selection:** Surgery, long-term antibiotic prophylaxis, noninvasive techniques, and any mix of therapies are also options for treating VUR. **Collection and Interpretation of Data:** Two authors searched the literature separately, determining research qualifications, assessing accuracy, and extracting and entering results. The odds ratio (OR) of these studies was used to construct the forest plot. The random-effects model was

used to pool the data. Also, the random-effects model was used with statistical significance at a p value < 0.05 to assess the difference in side effects after treatment of VUR using different modalities. **Results:** We found no statistically significant differences between surgery plus antibiotics and antibiotic alone-treated patients in terms of recurrent UTIs (OR = 0.581; 95% confidence interval [CI] 0.259–1.30), renal parenchymal defects (OR = 1.149; 95% CI 0.75–1.754), and renal scarring (OR = 1.042; 95% CI 0.72–1.50). However, the risk of developing pyelonephritis after surgical treatment of VUR was lesser than that in the conservative approach, that is, antibiotics (OR = 0.345; 95% CI 0.126–0.946), positive urine culture (OR = 0.617; 95% CI 0.428–0.890), and recurrent UTIs were more common in the placebo group than in the antibiotic group ($p < 0.05$; OR = 0.639; 95% CI 0.436–0.936) which is statistically significant. **Conclusion:** Based on current research, we recommend that a child with a UTI and significant VUR be treated conservatively at first, with surgical care reserved for children who have issues with antimicrobials or have clinically significant VUR that persists after several years of follow-up.

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Min Xie and Xiaogai Xu are both the first authors, they contributed equally.

Introduction

Urinary tract infection (UTI) is the most common infection among children [1, 2]. One of the most common causes of problems related to the urinary tract among children is vesicoureteral reflux (VUR). VUR is the retrograde flow of the urine from the bladder to the ureter and renal pelvis [3]. Previous studies have shown that this is one of the most common predisposing factors for UTI. UTI combined with VUR is a risk factor for various renal problems like pyelonephritis, renal scarring, hypertension, and other renal parenchymal defects [4]. However, there is debate on the causal association between these entities, and data on the actual occurrence of clinically relevant VUR complications are scarce [3]. Due to the lack of objective data, most VUR management assessments have been based on expert views [4], and the superiority of either medical or surgical treatment in avoiding kidney damage has not been shown [5–8].

Although the precise incidence in the general infant population is uncertain, VUR is consistently observed in around a third of children with UTIs. In addition, UTI affects 5–10% of girls, while VUR affects 1–3% [2]. Thus, VUR is thought to predispose sufferers to UTIs involving the kidney material, leading to permanent renal damage. While recent findings from a prospective cohort study suggest that adverse effects of renal damage associated with UTI are significantly lower, retrospective analyses of selected patients with renal scarring report hypertension in about 20% of patients and chronic kidney disease 10% of patients [4–8].

The prevention of UTI-induced disruption has become the primary treatment technique for children with VUR. Surgical reflux correction and long-term antibiotic prophylaxis, either alone or in combination, have been tried. Latest, less intrusive procedures such as endoscopic periureteric injections of polydimethylsiloxane (Macropastique), dextranomer/hyaluronic acid copolymer (Deflux), or glutaraldehyde cross-linked bovine collagen have been evaluated in addition to the traditional Politano-Leadbetter and Cohen surgical techniques [9–12].

Because VUR is a widespread childhood issue, there is much debate over the proper treatment. The Pediatric Vesicoureteral Reflux Guidelines Panel [1] published a study that resulted in few clinical suggestions focused on empirical proof of efficacy, instead of focusing on “panel advice” for most decisions.

Rationale

Due to a lack of scientific data, management decisions on VUR have primarily been focused on expert views, and the superiority of either medical or surgical treatment in avoiding kidney damage has not been shown. We used renal parenchymal defects, renal scarring, pyelonephritis, and recurrence of UTI as endpoints in a meta-analysis to evaluate surgical and conservative treatment effectiveness, that is, the prevalence of side effects. We tried to see if any research could help a clinician choose between these treatment options. This research aimed to assess the evidence for the advantages and risks of the currently available treatment methods, including operative, non-operative, and no intervention.

Objective

The objective of this study was to assess the data for the advantages and drawbacks of various key VUR care options.

Materials and Methods

We followed the PRISMA normative recommendations in this study with the registration number PU # RC/IRB/2020/1036.

Eligibility Criteria for Considering Studies

Any therapy in primary VUR was tested in randomized controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation of care was achieved through alternation, alternative medical history, date of birth, or other predictable methods). The articles were reviewed from the title or abstract. Case reports, solely neonatal or adult studies, reviews, editorial commentaries, animal studies, articles about secondary or sibling VUR, and publications concerned exclusively with UTI were excluded. The articles concerned only with children, with at least one defined treatment group, addressed the various side effects, and written in English with no other limiting factor were used in finalizing the studies.

Data Search

The authors searched the medical literature on the topic was extensively searched in MEDLINE, EBSCO, and UPTODATE databases from 1985 to 2020. There was no restriction on the selection of articles based on their year of publication. The author's used the MESH terms to search for the topic. The keywords used were urogenital abnormalities, VUR, renal parenchymal defects, UTIs, renal scarring, pyelonephritis, antibiotic, surgical, and endoscopy.

Selection Process

Information on the following aspects was included in the meta-analysis:

- Recurrent UTI after use of antibiotics compared to a placebo group
- Recurrent UTI after endoscopic surgery compared to antibiotics
- Positive urine culture after surgery and antibiotics compared to administration of antibiotics alone

- Renal parenchymal defects after endoscopic surgery compared to antibiotics
- Renal scarring after endoscopic surgery compared to antibiotics
- Pyelonephritis after endoscopic surgery compared to antibiotics

The primary search yielded 10,355 results. Articles were debarred based on the exclusion criteria. These included 57 articles, out of which 20 articles were included in data analysis. The selection of articles was made after critical evaluation by a panel of 3 experts. They were given a vital evaluation checklist for the article review. The final selection was based on the review by a panel of experts. Details of the number of articles included are given in Figure 1.

At least 3 reviewers independently screened abstracts received from the above searches for selection (M.X., X.X., and H.X.). Any discrepancies were worked out with the help of a fourth author (Z.C.). When the suitability of an essay was questioned, or there was no abstract available, the entire article was retrieved. Over selection was preferred in all situations to prevent applicable missing studies and ensure that reference lists could find additional studies. Where applicable, authors were contacted to collect raw or incomplete data.

A random-effects model was used to obtain overall estimates of event probabilities (e.g., recurrent UTIs, renal scars, renal parenchymal defects, etc.). After tabulating the data, individual study estimates were obtained with the overall forecast and observation characteristics using the odds ratio (OR). Differences between or among specific groups were assessed using the Z test. Statistical significance was set at 0.05 for comparing the 2 groups. Forest plots were used to represent individual study estimates (points) and their 95% confidence intervals (CIs), together with the overall assessment. The meta-analysis was carried out using Comprehensive Meta-Analysis Software Version 3.

Results

Literature Search

The primary search yielded 10,355 results. Articles were debarred based on the exclusion criteria. These included 57 articles, out of which 20 articles were included in data analysis. The selection of articles was made after critical evaluation by a panel of 3 experts. They were given a vital evaluation checklist for the article review. The final selection was based on the review by a panel of experts. Details of the included studies are given in Table 1.

Risk of Bias

Five studies found the treatment distribution process to be satisfactory. Just 2 analyses found that radiological results were assessed without knowing which treatment groups they were in. In 4 trials, there was no intention-to-treat analysis; in the other studies, it was unable to decide if the analysis was conducted on an intention-to-treat basis. Losses due to follow-up were generally poor, ranging between 0 and 2% after 1–2 years and 9 and 42% after 4–10 years.

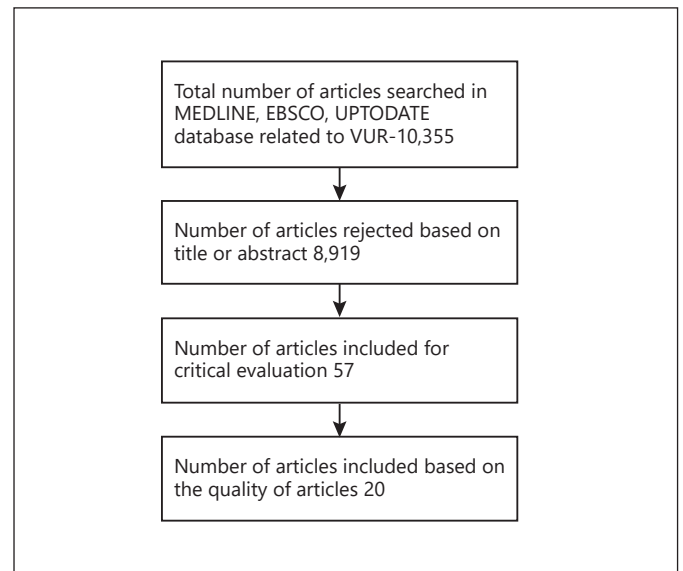


Fig. 1. The details of the number of articles included.

Effects of Interventions

Recurrent UTI in Placebo versus Antibiotic Group

A total number of 8 studies were evaluated for the odds of developing recurrent UTIs in the treatment of VUR among pediatric patients with the help of a random-effects model. Cumulative statistics were significant at a 95% confidence level with $p < 0.05$ (0.021). On the left side, it favors treatment with antibiotics alone with a CI varying from 0.436 to 0.936 with an OR of 0.639, indicating that developing recurrent UTIs after antibiotics treatment for VUR was 0.639 times more than that in the placebo group (Fig. 2).

Positive Urine Culture after Surgery and Antibiotics Compared to Administration of Antibiotics Alone

A total of 7 studies were assessed for the odds of developing a positive urine culture between the 2 treatment modalities. Cumulative statistics were significant at a 95% confidence level with $p < 0.05$ (0.010). The cumulative statistics on the left side favor a combined approach of surgery and antibiotics compared to antibiotics alone, with an OR of 0.617 which indicates that a positive urine culture is more likely to develop in the surgery and antibiotics approach than antibiotics alone (Fig. 3).

Renal Parenchymal Defects after Endoscopic Surgery Compared to Antibiotics

Similarly, a total number of 4 studies were examined for evaluating the odds of developing renal parenchymal

Table 1. Details of included studies [9, 13–31]

S.No	Study	Year	Study design	OR	Adverse effects reported after VUR treatment	Comparison between
1	Reddy et al. [13]	1997	Randomized prospective study	7.174	UTIs	Antibiotics versus placebo
2	Garin et al. [14]	2006	Multicenter, randomized, controlled study	1.059	UTIs	Antibiotics versus placebo
				0.923	Renal scarring	Surgery versus conservative treatment
3	Pennesi et al. [15]	2008	Randomized, controlled study	1.313	UTIs	Antibiotics versus placebo
				1.014	Renal scarring	Surgery versus conservative treatment
4	Montini et al. [16]	2008	Multicenter, randomized, controlled, noninferiority trial	0.733	UTIs	Antibiotics versus placebo
5	Roussey-Kesler et al. [17]	2008	Prospective randomized study	0.970	Renal scarring	Surgery versus conservative treatment
6	Craig et al. [18]	2009	RCT	0.596	UTIs	Antibiotics versus placebo
7	Brandström et al. [19]	2010	RCT	0.990	Renal scarring	Surgery versus conservative treatment
				0.171	UTIs	Antibiotics versus placebo
				0.963	Renal scarring	Surgery versus conservative treatment
				0.526	UTIs	Surgery versus conservative treatment
				0.480	UTIs	Antibiotics versus placebo
8	Hoberman and Chesney [20]	2014	RCT	1.059	Positive urine culture	Surgery and antibiotics versus antibiotics
9	Holland et al. [21]	1982	Prospective randomized study			
				3.667	Renal parenchymal defects	Surgery versus antibiotics
10	BIRSG [22]	1987	Prospective trial	1.313	Positive urine culture	Surgery and antibiotics versus antibiotics
				0.866	Renal parenchymal defects	Surgery versus antibiotics
				0.352	Renal scarring	Surgery versus conservative treatment
11	Morris et al. [23]	1991	Prospective	0.733	Positive urine culture	Surgery and antibiotics versus antibiotics
12	Duckett et al. [24]	1992	Surgical results	0.596	Positive urine culture	Surgery and antibiotics versus antibiotics
				0.996	Renal parenchymal defects	Surgery versus antibiotics
13	Smellie et al. [25]	2001	Randomized trial	0.299	UTIs	Surgery versus conservative treatment
				0.605	Positive urine culture	Surgery and antibiotics versus antibiotics
14	Capozza and Caione [9]	2002	Randomized comparative	0.923	Pyelonephritis	Surgery versus conservative treatment
				0.171	Positive urine culture	Surgery and antibiotics versus antibiotics
15	Ausgabe [26]	1981	Prospective reflux study	0.480	Positive urine culture	Surgery and antibiotics versus antibiotics
				1.259	Renal parenchymal defects	Surgery versus antibiotics
16	Weiss et al. [27]	1992	Prospective trial	1.606	UTIs	Surgery versus conservative treatment
				0.745	Renal scarring	Surgery versus conservative treatment
				0.299	Pyelonephritis	Surgery versus conservative treatment
17	Olbing et al. [28]	1992	Randomized trial	0.836	Renal scarring	Surgery versus conservative treatment
18	Jodal et al. [29]	2006	Randomized trial	0.957	Renal scarring	Surgery versus conservative treatment
19	Teixeira et al. [30]	2017	Randomized trial	1.042	Renal scarring	Surgery versus conservative treatment
20	Dite et al. [31]	2017	Randomized trial	0.321	UTIs	Surgery versus conservative treatment
VUR, vesicoureteral reflux; UTIs, urinary tract infections; OR, odds ratio; RCT, randomized controlled trial.						

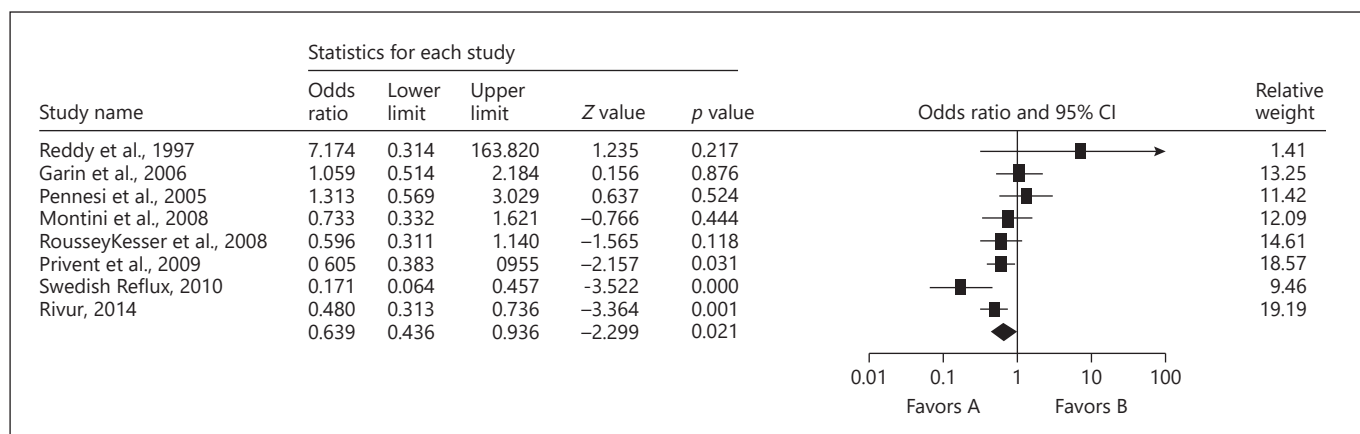


Fig. 2. Shows the forest plot between the chances of recurrent UTIs in comparison of antibiotics with placebo treatment for VUR. VUR, vesicoureteral reflux; OR, odds ratio; UTIs, urinary tract infections.

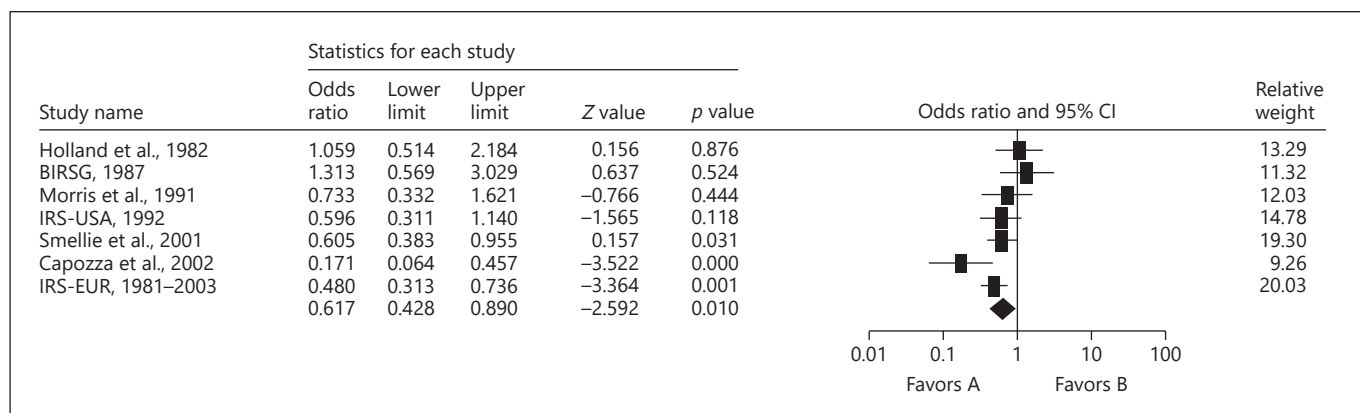


Fig. 3. Shows the forest plot for the positive urine culture report after treating VUR with a combination of surgery and antibiotics as compared to antibiotics alone. VUR, vesicoureteral reflux; OR, odds ratio.

defects in the 2 groups of surgery compared to antibiotics. Again, cumulative statistics were not significant at 95% confidence level with $p > 0.05$ (0.517), that is, there is no statistically significant difference existing in both treatment modalities for renal parenchymal defects with an OR of 1.149 which indicates that renal parenchymal defects are more likely to develop in the groups treated with surgery than antibiotics (Fig. 4).

Renal Scarring after Endoscopic Surgery Compared to Antibiotics

A total number of 4 studies were assessed for evaluating the odds of developing renal scarring among the 2 groups, that is, surgery versus no surgery. The cumulative statistics were not statistically significant at a 95% confidence level with $p > 0.05$ (0.827), that is, there is no dif-

ference in both the treatment modalities on renal scarring with an OR of 1.042, indicating that renal scarring is more likely to be present in the groups treated with surgery than conservative treatment (Fig. 5).

Recurrent UTI after Endoscopic Surgery Compared to Antibiotics

A total number of 4 studies were examined for evaluating the odds of developing recurrent UTIs among the groups, that is, surgery versus no surgery. The cumulative statistics were not statistically significant at a 95% confidence level with $p > 0.05$ (0.189), that is, there is no difference in both the treatment modalities for UTIs with an OR of 0.581 which indicates that UTIs are more likely to be present in the groups treated with surgery than conservative treatment (Fig. 6a).

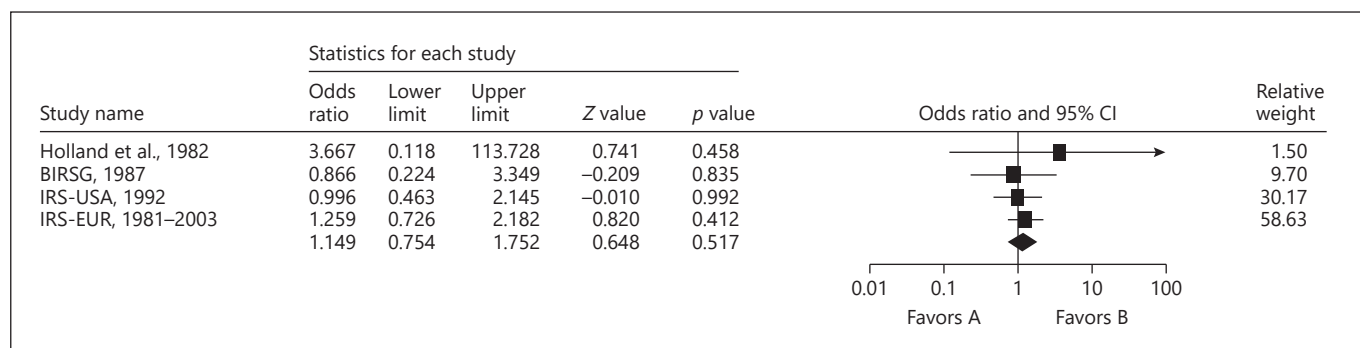


Fig. 4. Shows the forest plot for the renal parenchymal defects developed after treating VUR with surgery as compared to antibiotics alone. VUR, vesicoureteral reflux; OR, odds ratio.

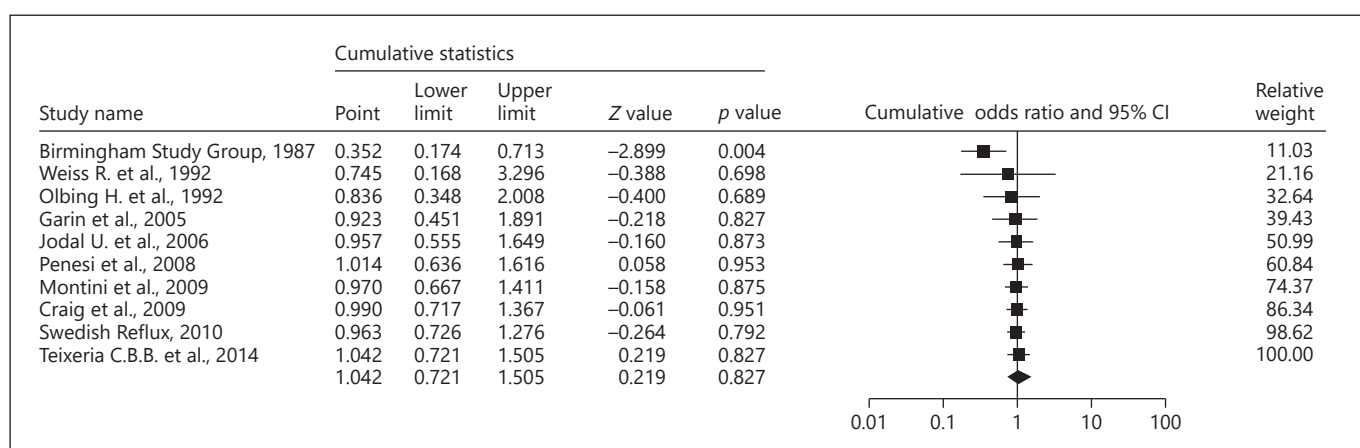


Fig. 5. Shows the forest plot for the renal scarring developed after treating VUR with surgery as compared to a conservative treatment approach. VUR, vesicoureteral reflux; OR, odds ratio.

Pyelonephritis after Endoscopic Surgery Compared to Antibiotics

The random-effects model was used to assess the 4 studies progressively for evaluating the odds of developing pyelonephritis in 2 groups, that is, surgery versus no surgery. The cumulative statistics showed a statistically significant $p < 0.05$ under the random-effects model, with CI varying from 12.6 to 94.6%. The point estimate (OR) was < 1 (0.345), indicating that pyelonephritis is 0.345 less likely to occur after the surgical treatment of VUR compared to the conservative treatment approach (Fig. 6b).

Discussion

We looked at many articles, but only a couple of them were appropriate for further study, and none of them covered any of the scientifically relevant endpoints. Several

trials focused on highly chosen patient samples, and the rest were historical, simply describing a collection of patients seen at the study institution. Treatment indications were not always given, and the patient population was rarely identified.

Just a few publications separately published statistics on the sexes, and the outcomes (kidney problems or VUR resolution) were frequently reported in terms of the number of kidneys, making it difficult to conclude what happened to the patients. In addition, any experiment was difficult to compare due to 4 different systems for scoring VUR. During follow-up, many did not monitor the resolution of VUR, and some did not rate the seriousness of the UTIs. We did not see any significant improvements in research architecture over time, unlike Jodal et al. [29], and the total importance of the publications was modest. Thus, the meta-analysis' limited strength is attributed in part to the fact that only 5 studies meet the criterion for

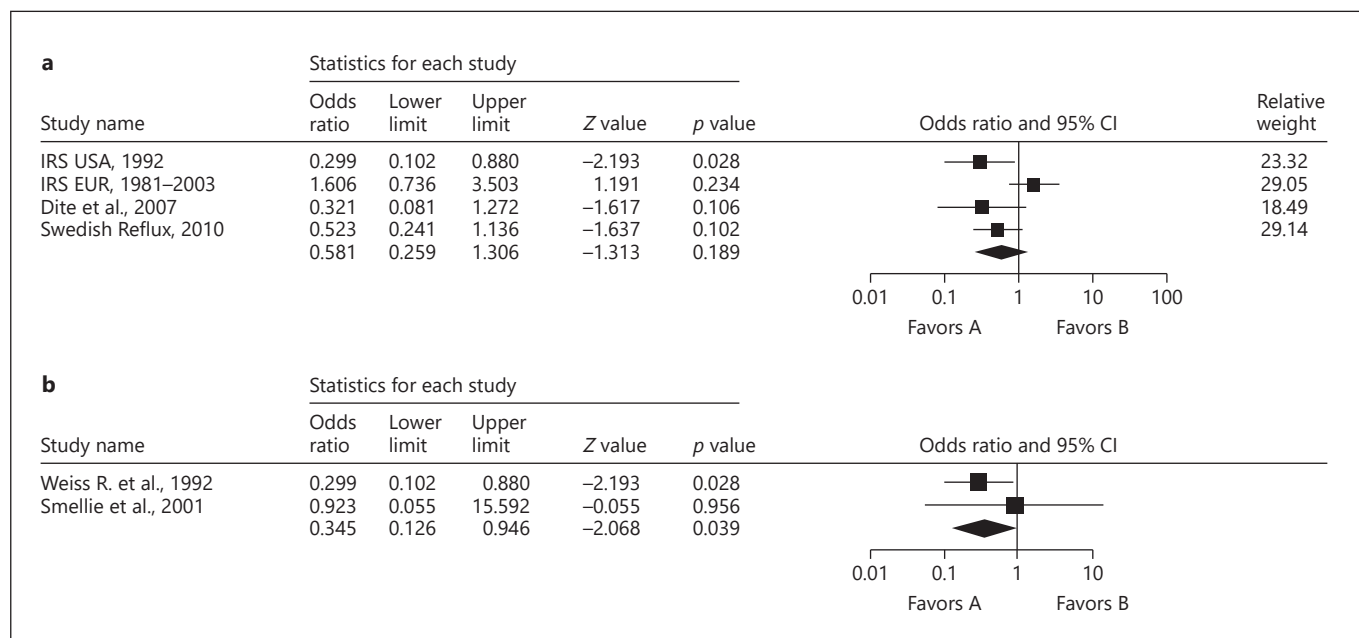


Fig. 6. a Shows the forest plot for the recurrent UTIs developed after treating VUR with surgery as compared to a conservative treatment approach. **b** Shows the forest plot for the pyelonephritis developed after treating VUR with surgery as compared to a conservative treatment approach. VUR, vesicoureteral reflux; OR, odds ratio; UTIs, urinary tract infections.

assessment, reflecting the unfortunate state of trials for the care of VUR in infants.

Antibiotic prophylaxis is most commonly used to treat recurrent UTIs among children with VUR based on the grading of VUR. However, the American Association of Pediatricians has issued guidelines to the community of pediatricians, suggesting that antibiotic prophylaxis may not be necessary and should be used judiciously to keep in mind the side effects of the same grading of VUR [32–35]. Garin et al. [14], in their randomized controlled study among 236 patients, also found that urinary antibiotic prophylaxis does not affect the severity of UTIs in their patients with mild/moderate VUR. It was also seen by Montini et al. [5], wherein there is a greater risk of UTI in children of younger age after the antibiotic prophylaxis treatment for VUR. Brandström et al. [19], during the Swedish reflux trial in children, showed that 19% developed recurrent UTIs after antibiotic prophylaxis and 23% developed after surgical intervention in the treatment for VUR, which was 3 times less than in those children not receiving the prophylaxis. The RIVUR study involved 607 children (558 girls and 49 boys) with Grade I–IV VUR. Recurrent UTIs developed in 39 (13%) out of 302 children who received prophylaxis, compared with 72 (24%) out of 305 who received placebo (relative risk

0.55, 95% CI 0.38–0.78) [20]. The present study also showed that the recurrent UTIs after antibiotic prophylaxis are lesser than that of the placebo group.

Continuous antibiotic prophylaxis is the most recommended treatment for correction of VUR. It consists of prescribing daily antibiotics at one-quarter to one-half the regular therapeutic dose. Trimethoprim-sulfamethoxazole, amoxicillin, and nitrofurantoin are the most commonly used CAP agents [36]. The present study shows that the chances of UTI after antibiotic treatment of VUR are less among pediatric patients than in a placebo group.

The surgical approach for treating VUR involves widening or changing the shape/angle of the ureter orifice for proper bladder filling via various techniques like open surgical ureteroneocystostomy, endoscopy, and laparoscopy. Hutch [37] first reported surgical correction in 77.7% of patients with VUR in 1952. Our meta-analysis shows that surgery successfully eliminates VUR, but there was no substantial difference between conservative and operative care in terms of recurrent UTIs, renal parenchymal defects, or renal scarring. Shannon and Feldman analyzed the findings of conservative and surgical care of VUR in a critical review of the literature. They concluded that, aside from eliminating reflux, surgery offered no

other short-term benefits according to our study. Antibiotics are just a small part of the image [38].

Smellie et al. [6] do not support the hypothesis that surgical correction of VUR improves renal function in children with the bilateral disorder, which was confirmed by various studies on the same topic [9, 21–23]. Similarly, our meta-analysis indicates that a positive urine culture is more likely to develop in the surgery and antibiotics approach than antibiotics alone.

The presence of recurrent UTIs after the surgical correction of VUR was also reported by Dite et al. [31] and Brandström et al. [19], which indicated that patients with surgical intervention are 0.351 and 0.526 times more likely to develop recurrent UTIs than patients given conservative treatment. However, no statistical difference was noted in terms of recurrent UTIs to occur after surgical treatment or conservative approach for treating VUR as shown in this meta-analysis.

Weiss et al. [27] showed 0.742 times more likely to develop renal scarring and 0.299 times more likely to develop pyelonephritis after surgical treatment than conservative choice. Surgery does provide a significant advantage over pyelonephritis, according to all 4 RCTs included in our meta-analysis. As pyelonephritis is more likely to affect the kidneys than lower level UTIs, this may be taken to mean that surgery could not be favored for avoiding recurrences of UTI. However, even when using kidney injury as an endpoint, the supremacy of surgery was not shown.

Surgery for VUR is an extensive procedure that may cause problems [12, 14, 29, 39], prompting doctors to look for alternative treatments. Our meta-analysis found that conservative management (except for the elimination of VUR) is similarly efficient and that when children are followed for 10 years, >70% of cases of dilating VUR can be resolved or increase dramatically with development [6, 7]. Antimicrobials, especially nitrofurantoin, have been shown to cause gastrointestinal side effects in children aged <2 years, with up to one-third of these infants discontinuing prophylaxis [8].

Endoscopic therapy could be a safe option for these cases, although rates of VUR correction with endoscopic procedures are lower than those recorded with open reimplantations [40]. It has also been noted that parents prefer antimicrobial prophylaxis in the care of VUR over either endoscopic or open surgical treatment. Also, 5 years of antimicrobial prophylaxis over open surgery and 3 years of prophylaxis over endoscopic correction of VUR seem to be preferred by parents of children with VUR [41].

The meta-analysis has multiple limitations like the articles did not focus on secondary VUR. Included studies have not considered the side effects of treatment options for correction of VUR on its grade, and no limiting factor based on the year of publication has been considered. There is no difference reported in surgical than that in conservative treatment in terms of recurrent UTIs, renal scarring, and renal parenchymal defects.

Conclusion

Based on the findings of our meta-analysis, we believe that conservative care is appropriate for the vast majority of children with VUR and that such children should be tracked for several years before undergoing corrective surgery. In addition, surgical correction of VUR should be treated if there are repeated breakthrough UTIs or if prophylactic antimicrobials are not accepted.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee of University of Electronic Science and Technology of China, Children's Hospital of Shanxi, the Third Affiliated Hospital of Zhengzhou University, and Peking University First Hospital with the reference number PU # RC/IRB/2020/1036 and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding for this study.

Author Contributions

M.X. contributed to the concept and designed the study, X.X. analyzed data; Z.C. collected the data and helped in data analysis; H.X. contributed to drafting of the manuscript.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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