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Effectiveness of various treatment modalities in children with vesicoureteral reflux grades II–IV: a systematic review and network meta-analysis

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ABSTRACT

Background Vesicoureteral reflux (VUR) is one of the most common risk factors of urinary tract infection (UTI) among children. Various treatment modalities including antibiotic prophylaxis, surgical or endoscopic corrections and conservative treatment were used depending on the severity of VUR. The aim of this study is to compare the effectiveness of these treatment modalities in children with VUR grades II–IV by conducting a systematic review and network meta-analysis.

Methods A systematic search from different databases was performed from their earliest records to December 2022 without any language restriction. Only randomised controlled trials were included in this study. Effectiveness of treatment modalities was mainly compared by UTI. Other outcomes for renal scarring and resolution by renal units were also measured between treatments.

Results A total of 11 studies with 1447 children were included in this study. While comparing with antibiotic prophylaxis in network meta-analysis for UTI recurrence, surgical treatment probably lowers the rate of UTI recurrence (Log OR −0.26, 95% CI −0.54 to 0.02, high quality). However, endoscopic treatment (Log OR 0.2, 95% CI −1.41 to 1.81, high quality) and conservative treatment (Log OR 0.15, 95% CI −0.45 to 0.75, high quality) revealed probably inferior to antibiotic treatment.

Conclusion Both pairwise and network meta-analytic results probably showed no difference between the treatments in terms of their impact on UTI recurrence, progression of previous renal scars, or formation of new renal scars in children with VUR grades II–IV. These findings may offer a better understanding of each treatment and evidence-based suggestions for the choice of treatment, which should be individualised and based on the patient's risk factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Reimplantation surgery provides a significantly better reflux resolution in children with vesicoureteral reflux (VUR).

WHAT THIS STUDY ADDS

⇒ There is no significant difference in urinary tract infection (UTI) recurrence rate, renal scar progressions and new renal scar formation in VUR grades II–IV between antibiotic prophylaxis, endoscopic surgery and reimplantation surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The choice of treatment should be individualised and risk-based approach. Physicians' and parents' preference should also be considered because of no significant differences between antibiotic prophylaxis, endoscopic surgery and reimplantation surgery in preventing UTI recurrence and renal scarring.

INTRODUCTION

Primary vesicoureteral reflux (VUR), the reflux of urine into the ureter or the kidney due to anti-reflux failure in vesicoureteral junction,[1] is a common risk factor of urinary tract infection (UTI) among children. The incidence of VUR among normal children is 0.5%–3%.[2] However, in those with UTI combined with VUR, the incidence rises to 30%–40%.[3 4] It is also a potential risk factor for various renal problems like pyelonephritis, renal scarring and chronic kidney disease.[5]

The grading of VUR is mostly defined by the use of radiographic classification based on the degree of filling and dilatation of the ureter, renal pelvis and calyces by the International Reflux Study group.[6] Voiding cystourethrogram is the gold standard for diagnosing VUR and defining its severity. The severity of VUR can also be easily assessed with distal ureter diameter ratio and VUR index score which can also predict for resolution.[7–9]

Spontaneous resolution of VUR can be observed in about more than 80% of grades I and II, around 45% of grade III, and less than 10% of grades IV and V.[10] Various treatment modalities including antibiotic prophylaxis

(AbxP), surgical (Sx Rx) or endoscopic corrections (Endo Rx), and conservative treatment without antibiotic prophylaxis (no AbxP) are used depending on the severity of VUR and physicians' preference.[11] Each treatment's effectiveness varies in preventing UTI and renal damage. Success rate also differs in each surgical correction method.[12 13] With good resolution rates, non-operative management, such as AbxP and no AbxP, are preferred treatments for low-grade VUR. However, Sx Rx is reserved for high-grade VUR due to a potential risk of renal damage.[14]

Previous meta-analytic studies[15–17] examined treatments mostly for low grades (I, II) and high grades (III, IV, V). However, in practice, children with grade V VUR is associated with a very high risk of recurrent UTI and renal scarring, and therefore, AbxP alone may not be sufficient for these patients and rarely enrolled in randomised controlled study. On the contrary, surgery is rarely used to treat grade I VUR patients. Having the high probability of rapid spontaneous resolution in VUR grade I, and concerning the high incidence of associated renal dysplasia or potential risk of renal damage in VUR grade V, the choice of treatment for these two grades is clear and more standardised. Therefore, most randomised controlled trials (RCTs) comparing AbxP, Endo Rx, or reimplantation include VUR grades II–IV patients. Herein, the aim of this study is to compare the effectiveness of these treatment modalities in managing children with VUR grades II–IV by conducting a systematic review and network meta-analysis.

METHODS

Search strategy

A systematic search was conducted in different databases including PubMed, Embase and Google scholar using both free text and MESH terms (VUR; vesicoureteral reimplantation; endoscopic treatment or AbxP). All databases were searched from their inceptions to December 2022 without any language restriction. The search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Involving a Network Meta-Analysis statement. The number of included and excluded studies was reported at each stage.

Selection criteria

Abstracts of the identified articles were manually reviewed, and full texts were assessed for those without clear eligibility. Only were RCT studies comparing any two of four treatments (vesicoureteral reimplantation, endoscopic treatment, AbxP, or surveillance with no AbxP) for managing primary VUR grades II–IV included in this study. Studies which examined treatments for VUR grades I–V and provided separate results for each grade were also eligible for inclusion.

Articles were excluded if treatment outcomes were not directly compared or if duplicate data on the same cohort were reported. Studies with primary VUR grade I or V and those with secondary VUR, such as posterior urethral valves, neurological abnormalities, other urological abnormalities, and kidney transplants, were also excluded.

Treatment modalities

Different treatment modalities for VUR grades II–IV reported in the included studies were AbxP, no AbxP, Sx Rx and Endo Rx.

Data extraction

Two investigators (C-LC and C-HC) extracted the data from each eligible study, including UTI, renal scarring for both old lesion progression and new scars formation, as well as resolution of VUR by cases and renal units. Another four investigators (C-KH, S-SDY and S-JC) checked the accuracy of extracted data, and a custom piloted spreadsheet was used for comparing those data for each variable of interest.

Outcomes

Primary outcome was to compare the rate of UTI according to the criteria defined by each study between treatment modalities.

Secondary outcomes were the rate of worsening of previous renal scars (ie, progression of old lesions) and formation of new renal scars usually followed by technetium-99 m-labelled dimercaptosuccinic acid (99mTc-DMSA) scintigraphy and also the resolution rate of VUR.

Risk-of-bias assessment

The Cochrane Collaboration risk of bias tool (RoB2) was used, and risks of bias, such as selection, performance, detection, attrition and reporting bias, were evaluated for each included study. Each item was rated as either low risk of bias, some concern (either lack of information or uncertainty over the potential for bias) or high risk of bias.

Statistical analysis

Pairwise comparisons between studies were performed by RevmanV. 5.4 software (www.cochrane.org), and R program software was used for conducting network meta-analysis. Frequentist model was adopted using netmeta package for estimating each treatment's effect. The statistical heterogeneity between the studies was measured by I^2 and Q_{total} showing the overall inconsistency in the network. Network consistency was checked with netsplit method. We conducted a pooled analysis of dichotomous outcomes using ORs for pairwise comparisons and ORs in logarithmic scale (log ORs) for comparisons in network meta-analysis. Random-effect method was used to overcome the high heterogeneity between studies.

Certainty of the evidence

The certainty of the results from both pairwise comparisons and network meta-analysis was accessed

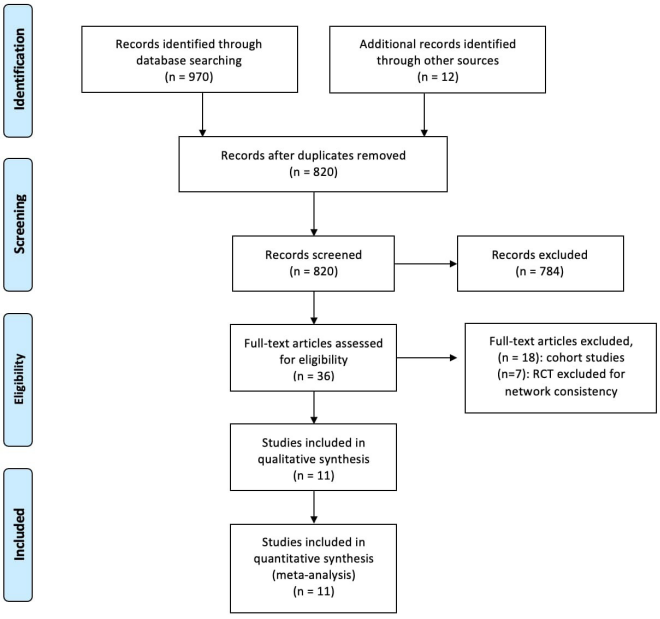

Figure 1 Research flow chart. RCT, randomised controlled trial.

with the methods provided in GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) handbook. Overall certainty of evidence was based on risk of bias, inconsistency, indirectness, imprecision and publication bias. Each result was graded into high, moderate, low or very low certainty.

Patient and public involvement statement

Patients or the public were not involved in the conduct of this systematic review and network meta-analysis study. The analyses were restricted to studies on children with VUR grade II–IV. The main target audience includes paediatricians, urologists, nephrologists and clinicians who have special interest in children with VUR.

RESULTS

Search strategy and study characteristics

The selection of articles was conducted according to the PRISMA guidelines, and a total of 820 studies were initially selected. A final sample of 11 studies including 1447 children with VUR grades II–IV were included, and the detailed process of selection is demonstrated in figure 1. All 11 studies were RCTs and all of which were published in English language. The oldest age of enrolled children was 18 years. Follow-up periods varied from 1 to 5 years. Characteristics of the included studies are summarised in table 1.

Risk of bias

Nearly half of the included studies reported unclear information about randomisation, allocation and blinding of outcome assessment. Two studies[18 19] had severe missing outcome data, and they were rated as high risk of bias in missing outcome data. Half of the included studies were considered for some concern as having bias in selection of reported results. For the overall bias, approximately 20% of the included studies were considered having a high risk of bias, and the results were summarised in figure 2A and B.

Evaluation of inconsistency and fitness of the model of the network meta-analysis

The network evidence of UTI for four treatment modalities was demonstrated with network graph (figure 3) including a total of nine studies. Our model showed two strong arms (AbxP vs no AbxP and AbxP vs Sx Rx) each including three studies, and it consisted of a closed loop between AbxP, Sx Rx and Endo Rx. Both results of direct and indirect methods calculated by the netsplit method did not show a significant difference between them. Therefore, no inconsistency was found in our model. For the fitness of model, only the studies which reported the outcomes of VUR grades II–IV were included, and fixed

Table 1 Study characteristics of included studies

Author/year	Country	VUR grade	Age	Follow-up	UTI definition	Comparisons
Hari 2015[20]	India	VUR grade III, IV	<12 years	1 year	(+) UC	AbxP versus no AbxP
Craig 2009[21]	Australia	VUR grade III, IV	<18 years	1 year	(+) UC	AbxP versus no AbxP
Pennesi 2008[22]	Italy	VUR grade II, III, IV	<2.5 years	4 years	Febrile UTI	AbxP versus no AbxP
Olbing 1992[18]	Germany	VUR grade III, IV	<11 years	5 years	No information	AbxP versus Sx Rx
Jodal 2006[19]	US	VUR grade III, IV	<11 years	5 years	(+) UC	AbxP versus Sx Rx
Weiss 1992[23]	US	VUR grade III, IV	< 10 years	4.5 years	No information	AbxP versus Sx Rx
BRSG 1983[24]	UK	VUR grade III or grade II with scarring	>1 year	2 years	(+) UC	Sx Rx versus AbxP
Garcia-Aparicio 2013[25]	Spain	VUR grade II, III, IV	>1 year	5 years	No information	Endo Rx versus Sx Rx
Capozza 2002[26]	Italy	VUR grade II, III, IV	>1 year	1 year	(+) UC	Endo Rx versus AbxP
Brandström 2011[27]	Sweden	VUR grade III, IV	1–2 years	2 years	Febrile UTI	Endo Rx versus AbxP versus no AbxP
Salih 2021[28]	Egypt	VUR grade III, IV	10 years	2 years	No information	Endo Rx versus Sx Rx

AbxP, antibiotic prophylaxis; Sx Rx, surgical treatment; Endo Rx, endoscopic treatment; UC, urine culture; UTI, urinary tract infection; VUR, vesicoureteral reflux.

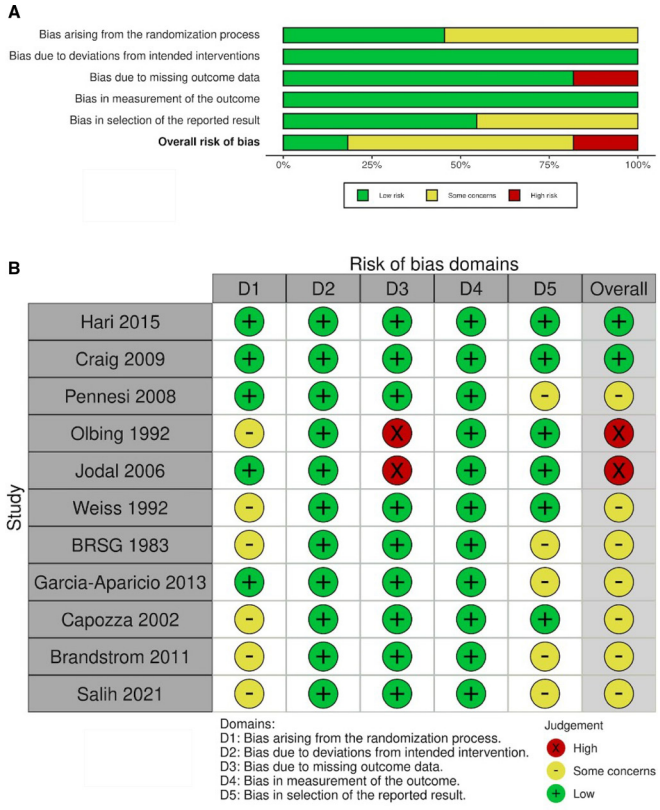

Figure 2 (A) Risk of bias graph: each risk of bias component displayed as percentage across papers. (B) Risk of bias summary: each risk of bias component for each paper.

effect model was used due to overall low heterogeneity among studies (Q value=0.91).

Synthesis of results

In this study, the effectiveness of treatment modalities was pooled analysed with primary outcomes (UTI) simultaneously measured by network meta-analysis. Other outcomes such as renal scarring and resolution by renal units (RRU) were only analysed by pairwise meta-analysis due to limited studies between treatments.

Urinary tract infection

A total of 9 studies[19–27] including 1013 participants reported the incidence of post-treatment UTI. The definitions of UTI were positive urine culture and symptomatic or febrile UTI. Some studies did not report information about UTI definition.

Pairwise comparisons of UTI between different treatment modalities

There was no significant difference in UTI recurrence among the treatment modalities. Sx Rx was associated with less UTI than AbxP, but the difference was not significant (OR=0.75, 95% CI 0.43 to 1.29, p=0.3). Endo Rx showed a higher risk of UTI than AbxP, but the difference was not significant (OR=2.03, 95% CI 0.89 to 4.64, p=0.09). Finally, there was no significant difference in UTI recurrence between AbxP or no AbxP (OR=1.07, 95% CI 0.51 to 2.24, p=0.86). All results for each treatment comparison are reported in table 2.

Results from network meta-analysis

Sx Rx showed the lowest risk of UTI compared with other treatments reporting in figure 4. However, the mixed comparison results were not significant with low heterogeneity.

Progression of old lesions

A total of four studies[18 22–24] were pooled for the analysis. Three studies compared AbxP and Sx Rx, and one compared AbxP and no AbxP. The pooled result showed that AbxP had potential for more progression of old lesions than Sx Rx (OR=1.23, 95% CI 0.79 to 1.93, p=0.36), but the result was not significant.

Formation of new renal scar

A total of 3 studies[18 23 27] with 641 participants were included. Two studies comparing AbxP and Sx Rx were pooled for pairwise comparison, and no significant result was found between them (OR=0.86, 95% CI 0.51 to 1.44, p=0.56). Another study compared AbxP, no AbxP and Endo Rx, and the results for these comparisons are reported in table 2.

Resolution by renal units

Of 4 studies[24–26 28] which reported corrected VUR by renal units, 2 studies consisting of 160 participants compared Sx Rx and Endo Rx. The other two studies compared Sx Rx and AbxP as well as Endo Rx and AbxP. Sx Rx showed a significantly better resolution rate of VUR than Endo Rx (OR=5.02, 95% CI 1.47 to 17.13, p=0.01). Both Sx Rx and Endo Rx showed better resolutions than AbxP, and the results are reported in table 2.

Complications

Most of the included studies did not report about complications except two studies.[19 25] Ureteral stricture is one of possible complications of Sx Rx. Long-term report of IRS

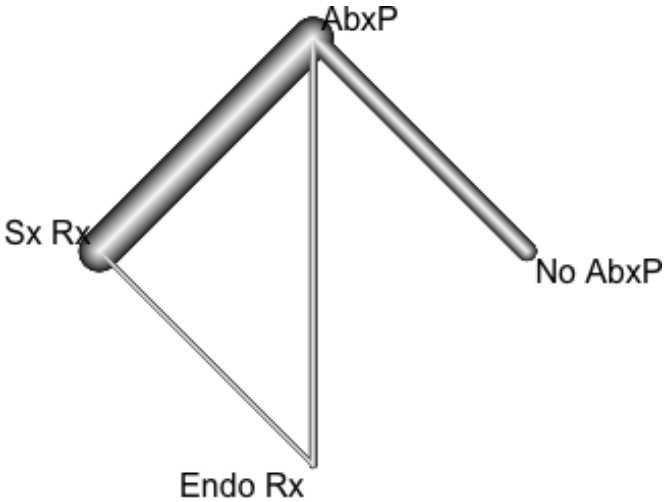

Figure 3 Network graph of each treatment for urinary tract infection.

Table 2 Results for pairwise comparisons of different treatment modalities

Outcomes	Treatment comparisons Treatment (1) versus (2)—references of included studies	Treatment (1) Total E/C (n/n)	Treatment (2) Total E/C (n/n)	OR (95% CI)
UTI	Sx Rx versus AbxP[20–22]	50/238	63/235	0.75 (0.43 to 1.29)
	Endo Rx versus AbxP[26 27]	20/105	10/90	2.03 (0.89 to 4.64)
	AbxP versus No AbxP[19 23 24]	26/152	24/145	1.07 (0.51 to 2.24)
	Endo Rx versus Sx Rx[25]	2/22	0/19	Not estimable
Progression of old lesions	AbxP versus Sx Rx[18 23 24]	52/270	43/264	1.23 (0.79 to 1.93)
	AbxP versus No AbxP[22]	1/50	9/50	0.09 (0.01 to 0.76)
Formation of new renal scars	AbxP versus Sx Rx[18 23]	33/223	36/215	0.86 (0.51 to 1.44)
	AbxP versus No AbxP[27]	0/69	9/68	Not estimable
	AbxP versus Endo Rx[27]	0/69	6/66	Not estimable
	Endo Rx versus No Abxb[27]	6/66	9/68	0.66 (0.22 to 1.96)
RRU	Sx Rx versus Endo Rx[25 28]	77/80	66/80	5.02 (1.47 to 17.13)
	Sx Rx versus AbxP[24]	67/69	17/65	94.59 (20.87 to 428.74)
	Endo Rx versus AbxP[26]	40/52	10/30	8.33 (3.14 to 22.13)

AbxP, antibiotic prophylaxis; E/C, events/cases; Endo Rx, endoscopic treatment; RRU, resolution by renal units; Sx Rx, surgical treatment; UTI, urinary tract infection.

study showed postoperative unilateral obstruction (6.6%, 10 in 151 patients) in which 7 patients (4.7%) needed further surgery.[19] Garcia-Aparicio *et al* also reported mild postoperative complications with haematuria (5.2%) and bladder spasm (5.2%).[25]

Certainty of the evidence

About two-third of the results from pairwise comparison were rated as moderate certainty as there were high risk of bias in randomisation process and outcome data. Overall certainty of the evidence and summary of findings table for pairwise comparison were presented in table 3. For network meta-analysis, only surgical treatment was found having moderate certainty and the rest having high certainty. Certainty of evidence for each treatment was integrated with the results and the overall summary of findings were reported in table 4.

DISCUSSION

To our knowledge, this is the first network meta-analysis that compared different treatment modalities for patients with VUR grades II–IV. The effectiveness of each treatment in preventing the occurrence of post-treatment UTI was simultaneously compared by conducting network meta-analysis. Sx Rx showed the best outcome

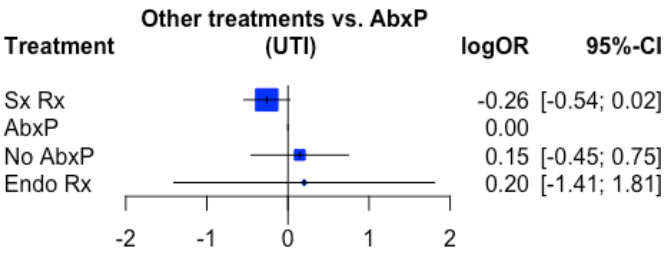

Figure 4 Comparison of urinary tract infection (UTI) recurrence after each treatment of vesicoureteral reflux (VUR).

in reducing post-treatment UTI among patients with VUR grades II–IV followed by AbxP, no AbxP and Endo Rx consecutively. However, mixed comparison results showed no significant differences. Pairwise comparisons for post-treatment UTI, progression of old lesions and formation of new renal scar showed no significant differences between the treatment modalities. However, Sx Rx provided a better resolution rate of VUR grades II–IV than Endo Rx and AbxP.

Children with VUR have a high spontaneous resolution rate within the first 4–5 years of life.[29 30] Male sex, young age, unilateral VUR have good resolution rate. Besides, it is also believed that VUR alone is not likely to cause renal damage without the presence of UTI.[31] Risk factors for UTI include young age, high-grade VUR, female sex and circumcision status in boys. Presence of bladder bowel dysfunction is also one of the important factors that influence VUR resolution rate and increase UTI risk.[32]

ABxP is commonly used for children with VUR to prevent UTI recurrence. However, several studies have examined age, gender and VUR severity to determine the efficacy of AbxP, and the results remain controversial. Swedish reflux study[27] and randomised intervention for children with vesicoureteral reflux trial[33] supported using AbxP because of its significant reduction in UTI recurrence, but PRIVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts) study[21] found a limited effect of AbxP. A recent meta-analysis[17] comparing all grades of VUR showed that recurrent UTI was less in AbxP than no AbxP group. In our study, there was no significant difference between AbxP and other treatments for UTI and renal damage. This may be due to differences in age, gender and VUR severity of included studies.

Antibiotic resistance is an emerging problem for AbxP,[34] and this may affect the treatment outcomes. Adverse effects of long-term antibiotic use such as allergic

Table 3 Summary of findings of GRADE analysis for pairwise comparisons

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with intervention*
UTI recurrence (AbxP vs No AbxP) follow-up: range 1–4 years	297 (3 RCTs)	High	**OR 1.07** (0.51 to 2.24)	166 per 1000	**10 more per 1000** (74 fewer to 142 more)
UTI recurrence (Sx Rx vs AbxP) follow-up: range 2–5 years	473 (3 RCTs)	Moderate	**OR 0.75** (0.43 to 1.29)	268 per 1000	**53 fewer per 1000** (132 fewer to 53 more)
UTI recurrence (Endo Rx vs AbxP) follow-up: range 1–2 years	195 (2 RCTs)	High	**OR 2.03** (0.89 to 4.64)	111 per 1000	**91 more per 1000** (11 fewer to 256 more)
UTI recurrence (Endo Rx vs Sx Rx) follow-up: median 1 year	41 (1 RCT)	High	Not estimable	0 per 1000	**0 fewer per 1000** (0 fewer to 0 fewer)
Progression of old lesion (AbxP vs Sx Rx) follow-up: range 2–5 years	534 (3 RCTs)	Moderate	**OR 1.23** (0.79 to 1.93)	163 per 1000	**30 more per 1000** (30 fewer to 110 more)
Progression of old lesion (AbxP vs No AbxP) follow-up: median 4 years	100 (1 RCT)	High	**OR 0.09** (0.01 to 0.76)	180 per 1000	**161 fewer per 1000** (178 fewer to 37 fewer)
Formation of new renal scars (AbxP vs Sx Rx) follow-up: range 4–5 years	438 (2 RCTs)	Moderate	**OR 0.86** (0.51 to 1.44)	167 per 1000	**20 fewer per 1000** (74 fewer to 57 more)
Formation of new renal scars (Endo Rx vs No AbxP) follow-up: median 2 years	134 (1 RCT)	Moderate‡	**OR 0.66** (0.22 to 1.96)	132 per 1000	**41 fewer per 1000** (100 fewer to 98 more)
RRU (Sx Rx vs Endo Rx) follow-up: range 2–5 years	160 (2 RCTs)	Moderate‡	**OR 5.02** (1.47 to 17.13)	825 per 1000	**134 more per 1000** (49 more to 163 more)
RRU (Sx Rx vs AbxP) follow-up: median 2 years	134 (1 RCT)	Moderate‡	**OR 94.59** (20.87 to 428.74)	262 per 1000	**709 more per 1000** (619 more to 732 more)
RRU (Endo Rx vs AbxP) follow-up: median 1 years	82 (1 RCT)	Moderate‡	**OR 8.33** (3.14 to 22.13)	333 per 1000	**473 more per 1000** (278 more to 584 more)

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Bold values were Odd ratios(OR) and risk differences for each treatment comparison.
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Unclear explanation of randomisation process in two studies and some missing data in one study.
‡Unclear explanation of randomisation process.
RCTs, randomised controlled trials; RRU, resolution by renal units; UTI, urinary tract infection.

reaction, weaken immune system and *Clostridium difficile* infection should also be considered. Becoming less effectiveness of AbxP, active surveillance without AbxP can be an alternative option. Being alert for febrile UTI and early treatment to prevent renal damage are necessary. Therefore, understanding and compliance of the parents play an important role for active surveillance.

Ureteral reimplantation has been used for decades with the most successful outcome for the correction of VUR. The principle of surgical correction is to mimic or strengthen the antireflux mechanism by creating the longer ureteral segment passing the tunnel between bladder mucosa and muscularis propria. Lich-Gregoir extravesical antireflux technique, Cohen intravesical reimplantation and Politano-Leadbetter combined intravesical and extravesical reimplantation technique are most commonly used methods.[35] Sx Rx included in our study are open ureteral reimplantation methods, mostly

Table 4 Summary of findings of GRADE analysis for network meta-analysis

Patient or population: VUR grades II–IV
Setting: various treatment modalities in children with VUR grade II–IV
Interventions: surgical, endoscopic and conservative treatment
Comparison: antibiotic prophylaxis
Outcome: UTI recurrence

Network geometry*

Total studies: 9 RCTs **Total participants: 1013**	**NMA estimate effect† (95% CI)**	**NMA Certainty in the evidence**	**Ranking‡ (P-score)**	**Interpretation**
Surgical treatment (Sx Rx)	−0.26 (−0.54 to 0.02)	Moderate§	0.85	Probably superior
Antibiotic prophylaxis (AbxP)	Reference comparator	Reference comparator	0.43	Reference comparator
Endoscopic treatment (Endo Rx)	0.2 (−1.41 to 1.81)	High	0.38	Probably inferior
Conservative treatment (No AbxP)	0.15 (−0.45 to 0.75)	High	0.31	Probably inferior

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
*Lines represent direct comparisons.
†Network estimate effects are reported as Log OR and the results are expressed in 95% CI since the frequentist model has been conducted.
‡Ranking is calculated by P-score by netrank function.
§Unclear explanation of randomisation process in two studies and some missing data in one study.
RCTs, randomised controlled trials; UTI, urinary tract infection; VUR, vesicoureteral reflux.

Cohen and Politano-Leadbetter technique. Despite a significant better RRU in Sx Rx, no significant difference was found in recurrent UTI and renal damage in our study. These results coincide with other meta-analyses.[16 17]

Another treatment option for VUR is Endo Rx which has been introduced over the last two decades.[36] Different bulking agents can be injected at ureteric orifice with the Traditional Subureteric Teflon Injection technique or hydrodistension implantation technique (HIT) including the double HIT.[37] However, the choice of bulking agents may impact the safety and efficacy of Endo Rx as granuloma formation due to foreign body reaction, migration from injection site and periureteric fibrosis. Dextranomer/hyaluronic acid showed low complication rates with short-term hematuria (0.2%–0.8%), ureteral obstruction (0.5%–1.3%), calcification (0.5%) and late ureteral implantation (2.7%).[38] Although Endo Rx showed significantly lower resolution rate than Sx Rx, it is less invasive and uses easier technique than Sx Rx. However, clinicians must balance risks and benefits of each procedure as well as their own surgical experiences.

Limitations of this study should be addressed. For low risks of bias, only randomised control studies were included in this study. As many studies did not report separate data for VUR grades II–IV, they were excluded from current study for network consistency and transitivity. Mixed treatment comparison could be performed by network meta-analysis only for UTI recurrence, and the rest parameters could only be compared with pairwise comparisons. Moreover, robotic-assisted surgery has been used to correct VUR in children with body weight>10 kg[39 40] while our study did not include it in this study. Therefore, future research should consider including robotic assisted surgery as one of the treatment modalities. Last, but not least, our study could not consider patients' age, febrile or symptomatic UTI, follow-up times, and publication years because of limited included studies.

CONCLUSION

The results from both pairwise and network meta-analyses suggest that there is probably no difference between the treatments concerning their impact on UTI recurrence, progression of previous renal scars, or the formation of new renal scars in children with VUR grades II–IV. These findings could offer valuable evidence-based insights for guiding treatment selection, emphasising the importance of individualised approaches based on each patient's specific risk factors.

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