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Effectiveness of Various Treatment Modalities in Patients with Vesicoureteral Reflux Grade II to IV: A Systematic Review and Network Meta-analysis

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Dear chief editors

Thank you for considering the manuscript of our "Effectiveness of various treatment modalities in patients with vesicoureteral reflux Grade II to IV: A systematic review and network meta-analysis" for publication.

This is a systematic review and network meta-analysis study comparing different treatments in patients with vesicoureteral reflux especially for Grade II to IV. To provide clinicians a better reference while choosing more effective or suitable intervention for patients suffering vesicoureteral reflux is what we sincerely aim at.

Sincerely yours,

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Effectiveness of Various Treatment Modalities in Patients with Vesicoureteral Reflux Grade II to IV: A Systematic Review and Network Meta-analysis

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval

This is a systematic review and network meta-analysis study. The Research Ethics Committee has confirmed that no ethical approval is required.

Conflict of interest

None.

Author Contributions Statement

C.L Chang and C.H Chen conceptualized and designed the study, performed data collection, data analysis and drafted the original manuscript. C.K Hsu, S.D Yang and S.J. Chang coordinated and supervised data collection, and critically reviewed the manuscript. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

What is already known on this topic – reimplantation surgery provides a significantly better reflux resolution in children with vesicoureteral reflux

What this study adds – There are no significant differences in 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 individualized and risk-based approach. Physicians' and parents' preference

should be also considered because of no significant differences between antibiotic prophylaxis, endoscopic surgery and reimplantation surgery in preventing UTI recurrence and renal scarring.

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 patients 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 randomized control trials were included in this study. Effectiveness of treatment modalities were 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. Surgical correction significantly provided a better resolution by renal unit than either endoscopic or antibiotic treatment. Pairwise comparisons for UTI, new renal scar formation, and progression of old lesions between different treatments showed no significant difference. Network meta-analysis for UTI revealed that surgical treatment had the least UTI recurrence compared with other treatments but the results were also not significant. Conclusions: Although surgical treatment provided a significantly better reflux resolution, each treatment did not significantly differ in having UTI recurrence, previous renal scars progression and new renal scars formation in VUR grades II-IV. The choice of treatment should be individualized and risk-based approach.

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 to 3%.[2] However, in those with UTI combined with VUR, the incidence rises to 30 to 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 (VCUG) 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, nonoperative 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 grade (I, II) and high grade (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 randomized 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 standardized. Therefore, most randomized control 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 patients with VUR grades II, III, and 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 (vesicoureteral reflux; vesicoureteral reimplantation; endoscopic treatment or antibiotic prophylaxis). 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 Involving a Network Meta-Analysis (PRISMA-NMA) statement. The number of included and excluded studies were 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, antibiotic prophylaxis, or surveillance with

no antibiotic prophylaxis) 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.L. Chang and C.H. Chen) extracted the data from each eligible study, including urinary tract infection (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.K Hsu, Stephen S.D. Yang, Y.C Tsai and S.J. Chang) 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 urinary tract infection (UTI) according to the criteria defined by each study between treatment modalities.

Secondary outcomes were the rate of worsening of previous renal scars (i.e. 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.[18] 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 Revman 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.[19] We conducted a pooled analysis of dichotomous outcomes using odds ratios (ORs) for pairwise comparisons and odds ratios in logarithmic scale (log ORs) for comparisons in network meta-analysis. Random-effects method was used to overcome the high heterogeneity between studies.

Results

Search strategy and study characteristics

The selection of articles was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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 Fig 1. All 11 studies were randomized control trials 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 summarized in Table (1).

Risk of bias

Nearly half of the included studies reported unclear information about randomization, allocation, and blinding of outcome assessment. Two studies[20, 21] 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 summarized in Fig 2 (a) 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 (Fig 3) including a total of 9 studies. Our model showed two strong arms (AbxP vs no AbxP and AbxP vs Sx Rx) each including 3 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 ($p = 0.99$). 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 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 analyzed with primary outcomes (urinary tract infection) simultaneously measured by network meta-analysis. Other outcomes such as renal scarring and resolution by renal units were only analyzed by pairwise meta-analysis due to limited studies between treatments.

Urinary tract infection

A total of 9 studies[21-29] 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 Fig (4). However, the mixed comparison results were not significant with low heterogeneity.

Progression of old lesions

A total of 4 studies[20, 24-26] 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[20, 25, 29] 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 (RRU)

Of 4 studies[26-28, 30] which reported corrected VUR by renal units, 2 studies consisting of 160 participants compared Sx Rx and Endo Rx. The other 2 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).

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 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.[31, 32] 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.[33] Risk factors for UTI includes 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.[34]

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 [29] and RIVUR trial[35] supported using AbxP because of its significant reduction in UTI recurrence, but PRIVENT study[23] 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,[36] and this may affect the treatment outcomes. Adverse effects of long-term antibiotic use such as allergic 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 intra- and extravesical reimplantation technique are most commonly used methods.[37] Sx Rx included in our study are open ureteral reimplantation methods, mostly Cohen and Politano-Leadbetter technique. Despite a significant better resolution by renal units 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].

Most of the included studies did not report about surgical complications except two studies.[21, 27] Ureteral stricture is one of possible complications of Sx Rx. Long term report of IRS study showed postoperative unilateral obstruction (6.6%, 10 in 151 patients) in which 7 patients (4.7%)

needed further surgery.[21] Garcia-Aparicio et al also reported mild postoperative complications with hematuria (5.2%) and bladder spasm (5.2%).[27]

Another treatment option for VUR is Endo Rx which has been introduced over the last two decades [38]. Different bulking agents can be injected at ureteric orifice with the Traditional Subureteric Teflon Injection (STING) technique or Hydrodistension implantation technique (HIT) including the double HIT.[39] 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 (Dx/HA) 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%).[40] 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 randomized 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 [41, 42] 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

Despite a significantly better resolution of VUR after surgical treatment, the evidence for UTI recurrence, previous renal scar progression and new renal scar formation showed no significant difference in VUR grades II-IV treated with various treatment modalities. The findings of this study may provide evidence-based suggestions for the choice of treatment which should be individualized and risk-based approach.

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Author Contributions Statement

C.L Chang and C.H Chen conceptualized and designed the study, performed data collection, data analysis and drafted the original manuscript. S.D Yang, C.K Hsu, Y.C Tsai, and S.J. Chang coordinated and supervised data collection, and critically reviewed the manuscript. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Legends to The Figures

Fig. 1 Research flow chart

Fig. 2(a) Risk of bias graph: each risk of bias component displayed as percentage across papers

Fig. 2(b) Risk of bias summary: each risk of bias component for each paper

Fig. 3 Network graph of each treatment for UTI

Fig. 4 Comparison of UTI recurrence after each treatment of VUR

Table 1 Study characteristics of included studies

Table 2 Results for pairwise comparisons of different treatment modalities

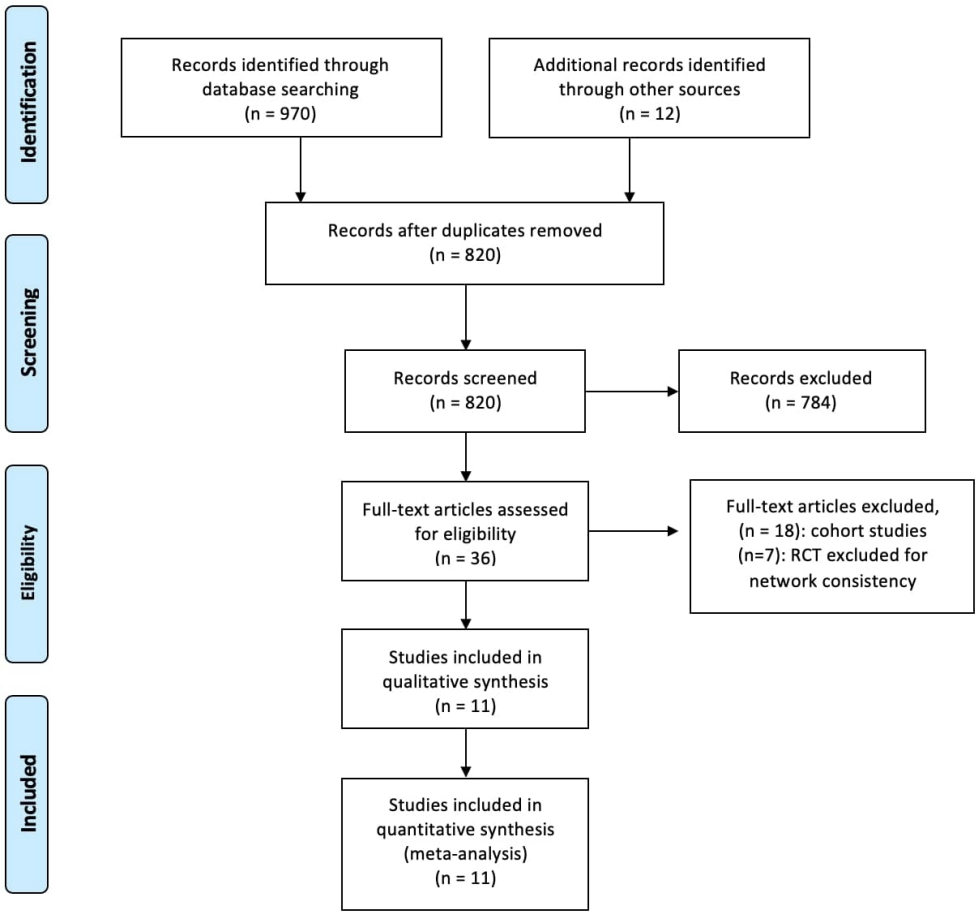
Declarations

Ethics approval

This is a systematic review and network meta-analysis study. The Research Ethics Committee has confirmed that no ethical approval is required and there is no clinical trial registration.

Conflict of interest

None.



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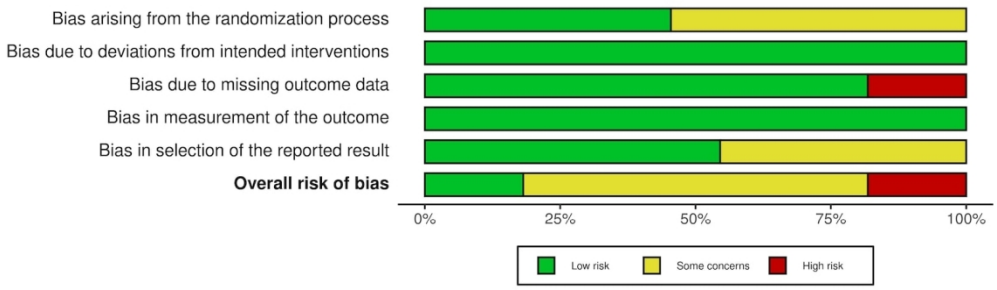

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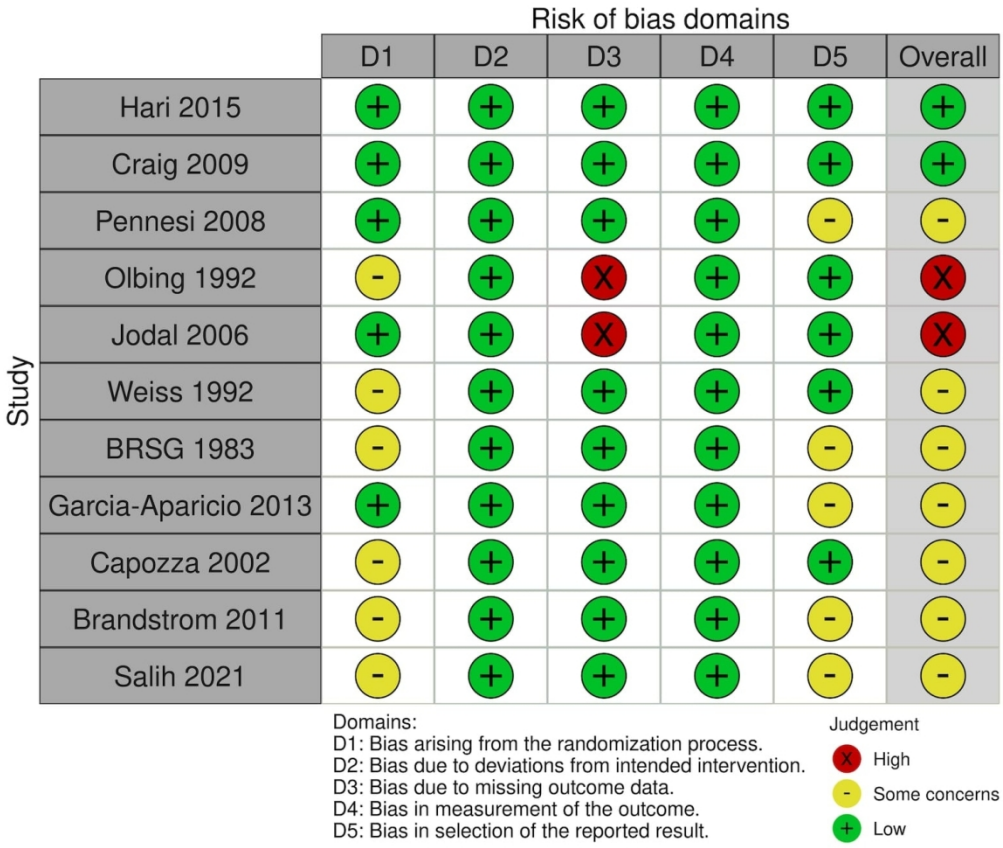

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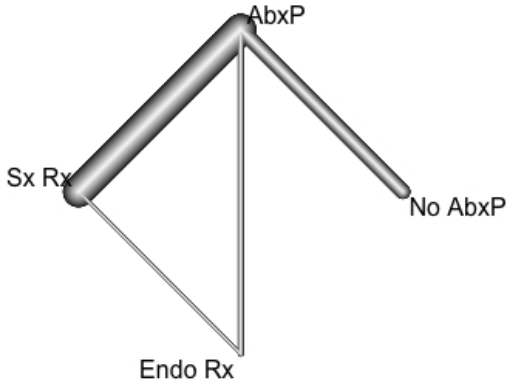

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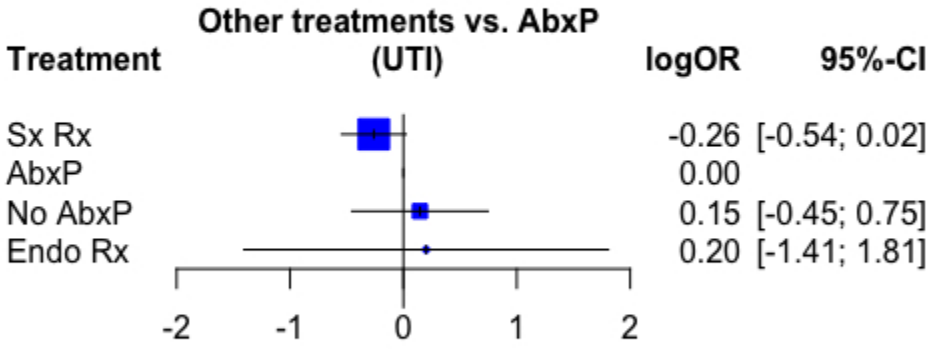

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Author/year	Country	VUR Grade	Age	Follow up	UTI definition	Comparisons
Hari 2015	India	VUR grade III, IV	<12 yrs	1 yr	(+) UC	AbxP vs no AbxP
Craig 2009	Australia	VUR grade III, IV	<18 yrs	1 yrs	(+) UC	AbxP vs no AbxP
Pennesi 2008	Italy	VUR grade II, III, IV	<2.5 yrs	4 yrs	Febrile UTI	AbxP vs no AbxP
Olbing 1992	Germany	VUR grade III, IV	<11 yrs	5 yrs	No information	AbxP vs Sx Rx
Jodal 2006	US	VUR grade III, IV	<11 yrs	5 yrs	(+) UC	AbxP vs Sx Rx
Weiss 1992	US	VUR grade III, IV	< 10 yrs	4.5 yrs	No information	AbxP vs Sx Rx
BRSG 1983	UK	VUR grade III or grade II with scarring	>1 yr	2 yrs	(+) UC	Sx Rx vs AbxP
Garcia-Aparicio 2013	Spain	VUR grade II, III, IV	>1 yr	5 yrs	No information	Endo Rx vs Sx Rx
Capozza 2002	Italy	VUR grade II, III, IV	>1 yr	1 yr	(+) UC	Endo Rx vs AbxP
Brandstrom 2011	Sweden	VUR grade III, IV	1-2 yrs	2 yrs	Febrile UTI	Endo Rx vs AbxP vs no AbxP
Salih 2021	Egypt	VUR grade III, IV	1- 10 yrs	2 yrs	No information	Endo Rx vs Sx Rx

Table (1) Study characteristics of included studies

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

Table (2) Results for pairwise comparisons of different treatment modalities

Outcomes	Treatment comparisons Treatment (1) vs (2)	Treatment (1) Total E/C (n/n)	Treatment (2) Total E/C (n/n)	OR (95%CI)
UTI	Sx Rx vs AbxP	50/238	63/235	0.75(0.43,1.29)
	Endo Rx vs AbxP	20/105	10/90	2.03(0.89,4.64)
	AbxP vs No AbxP	26/152	24/145	1.07(0.51,2.24)
	Endo Rx vs Sx Rx	2/22	0/19	4.76(0.21,105.47)
Progression of old lesions	AbxP vs Sx Rx	52/270	43/264	1.23(0.79,1.93)
	AbxP vs No AbxP	1/50	9/50	0.09(0.01,0.76)
Formation of new renal scars	AbxP vs Sx Rx	33/223	36/215	0.86(0.51,1.44)
	AbxP vs No AbxP	0/69	9/68	0.05(0,0.79)
	AbxP vs Endo Rx	0/69	6/66	0.07(0,1.21)
	Endo Rx vs No Abxb	6/66	9/68	0.66(0.22,1.96)
RRU	Sx Rx vs Endo Rx	77/80	66/80	5.02(1.47,17.13)
	Sx Rx vs AbxP	67/69	17/65	94.59(20.87,428.74)
	Endo Rx vs AbxP	40/52	10/30	8.33(3.14,22.13)

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

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***2-3***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2-3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***4***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	4

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***5***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	6
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	6
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5-6**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**-**

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Fig 3***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	*7*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**-**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***7-9***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	*7*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**-**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment*	12

		on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	-

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches.* Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

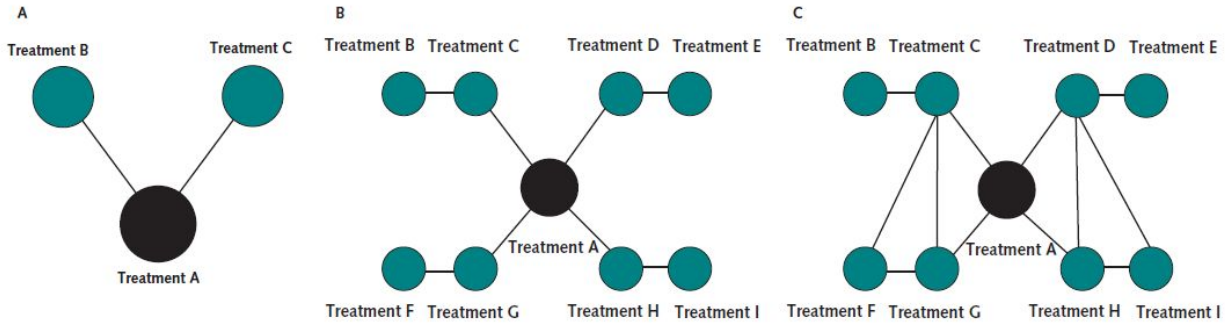
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

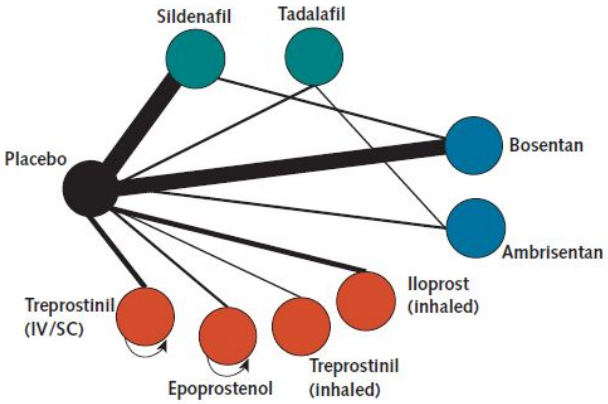
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

Appendix Figure 1A-1C

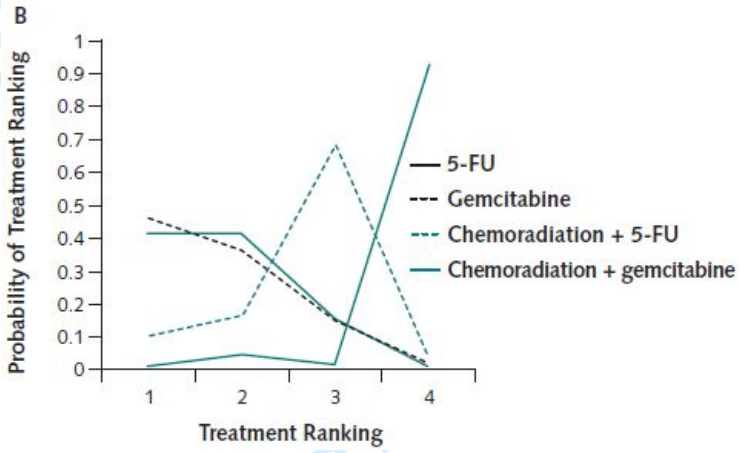


Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Cooresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93



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Effectiveness of Various Treatment Modalities in Children with Vesicoureteral Reflux Grade II to IV: A Systematic Review and Network Meta-analysis

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Effectiveness of Various Treatment Modalities in Children with Vesicoureteral Reflux Grade II to IV: A Systematic Review and Network Meta-analysis

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Competing interest

None.

Author Contributions Statement

C.L Chang and C.H Chen conceptualized and designed the study, performed data collection, data analysis and drafted the original manuscript. C.K Hsu, S.D Yang and S.J. Chang coordinated and supervised data collection, and critically reviewed the manuscript. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

What is already known on this topic – reimplantation surgery provides a significantly better reflux resolution in children with vesicoureteral reflux

What this study adds – There are no significant differences in 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 individualized and risk-based approach. Physicians' and parents' preference should be also considered because of no significant differences between antibiotic prophylaxis, endoscopic surgery and reimplantation surgery in preventing UTI recurrence and renal scarring.

ABSTRACT

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 patients with VUR grades II-IV by conducting a systematic review and network meta-analysis. A systematic search from different databases was performed from their earliest records to December 2022 without any language restriction. Only randomized control trials were included in this study. Effectiveness of treatment modalities were mainly compared by UTI. Other outcomes for renal scarring and resolution by renal units were also measured between treatments. 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. Surgical treatment was found to be more effective than other treatment options for resolving VUR. However, there was no significant difference between the treatments in terms of their impact on UTI recurrence, progression of previous renal scars, or formation of new renal scars. These findings provide evidence-based suggestions for the choice of treatment, which should be individualized and based on the patient's risk factors.

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 to 3%.[2] However, in those with UTI combined with VUR, the incidence rises to 30 to 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 (VCUG) 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, nonoperative 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 grade (I, II) and high grade (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 randomized 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 standardized. Therefore, most randomized control 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 patients with VUR grades II, III, and 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 (vesicoureteral reflux; vesicoureteral reimplantation; endoscopic treatment or antibiotic prophylaxis). 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 Involving a Network Meta-Analysis (PRISMA-NMA) statement. The number of included and excluded studies were 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, antibiotic prophylaxis, or surveillance with no antibiotic prophylaxis) 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.L. Chang and C.H. Chen) extracted the data from each eligible study, including urinary tract infection (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.K Hsu, Stephen S.D. Yang and S.J. Chang) 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 urinary tract infection (UTI) according to the criteria defined by each study between treatment modalities.

Secondary outcomes were the rate of worsening of previous renal scars (i.e. 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.[18] 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 Revman 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.[19] We conducted a pooled analysis of dichotomous outcomes using odds ratios (ORs) for pairwise comparisons and odds ratios in logarithmic scale (log ORs) for comparisons in network meta-analysis. Random-effects 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 were accessed with the methods provided in GRADE 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 to IV. The main target audience includes pediatricians, 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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 Fig 1. All 11 studies were

randomized control trials 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 summarized in Table (1).

Risk of bias

Nearly half of the included studies reported unclear information about randomization, allocation, and blinding of outcome assessment. Two studies[20, 21] 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 summarized in Fig 2 (a) 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 (Fig 3) including a total of 9 studies. Our model showed two strong arms (AbxP vs no AbxP and AbxP vs Sx Rx) each including 3 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 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 analyzed with primary outcomes (urinary tract infection) simultaneously measured by network meta-analysis. Other outcomes such as renal scarring and resolution by renal units were only analyzed by pairwise meta-analysis due to limited studies between treatments.

Urinary tract infection

A total of 9 studies[21-29] 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 Fig (4). However, the mixed comparison results were not significant with low heterogeneity.

Progression of old lesions

A total of 4 studies[20, 24-26] 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[20, 25, 29] 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 (RRU)

Of 4 studies[26-28, 30] which reported corrected VUR by renal units, 2 studies consisting of 160 participants compared Sx Rx and Endo Rx. The other 2 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.[21, 27] Ureteral stricture is one of possible complications of Sx Rx. Long term report of IRS study showed postoperative unilateral obstruction (6.6%, 10 in 151 patients) in which 7 patients (4.7%) needed further surgery.[21] Garcia-Aparicio et al also reported mild postoperative complications with hematuria (5.2%) and bladder spasm (5.2%).[27]

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 randomization process and outcome data. Overall certainty of the evidence and summary of findings table for pairwise

comparison was 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 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.[31, 32] 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.[33] Risk factors for UTI includes 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.[34]

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 [29] and RIVUR trial[35] supported using AbxP because of its significant reduction in UTI recurrence, but PRIVENT study[23] 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,[36] and this may affect the treatment outcomes. Adverse effects of long-term antibiotic use such as allergic 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 intra- and extravesical reimplantation technique are most commonly used methods.[37] Sx Rx included in our study are open ureteral reimplantation methods, mostly Cohen and Politano-Leadbetter technique. Despite a significant better resolution by renal units 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 [38]. Different bulking agents can be injected at ureteric orifice with the Traditional Subureteric Teflon Injection (STING) technique or Hydrodistension implantation technique (HIT) including the double HIT.[39] 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 (Dx/HA) 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%).[40] 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 randomized 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 [41, 42] 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

Surgical treatment was found to be more effective than other treatment options for resolving VUR. However, there was no significant difference between the treatments in terms of their impact on UTI recurrence, progression of previous renal scars, or

formation of new renal scars. These findings provide evidence-based suggestions for the choice of treatment, which should be individualized and based on the patient's risk factors.

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Author Contributions Statement

C.L Chang and C.H Chen conceptualized and designed the study, performed data collection, data analysis and drafted the original manuscript. S.D Yang, C.K Hsu and S.J. Chang coordinated and supervised data collection, and critically reviewed the manuscript. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Legends to The Figures

Fig. 1 Research flow chart

Fig. 2(a) Risk of bias graph: each risk of bias component displayed as percentage across papers

Fig. 2(b) Risk of bias summary: each risk of bias component for each paper

Fig. 3 Network graph of each treatment for UTI

Fig. 4 Comparison of UTI recurrence after each treatment of VUR

Table 1 Study characteristics of included studies

Table 2 Results for pairwise comparisons of different treatment modalities

Table 3 Summary of findings of GRADE analysis for pairwise comparisons

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

Table (1) Study characteristics of included studies

Author/year	Country	VUR Grade	Age	Follow up	UTI definition	Comparisons
Hari 2015[22]	India	VUR grade III, IV	<12 yrs	1 yr	(+) UC	AbxP vs no AbxP
Craig 2009[23]	Australia	VUR grade III, IV	<18 yrs	1 yrs	(+) UC	AbxP vs no AbxP
Pennesi 2008[24]	Italy	VUR grade II, III, IV	<2.5 yrs	4 yrs	Febrile UTI	AbxP vs no AbxP
Olbing 1992[20]	Germany	VUR grade III, IV	<11 yrs	5 yrs	No information	AbxP vs Sx Rx
Jodal 2006[21]	US	VUR grade III, IV	<11 yrs	5 yrs	(+) UC	AbxP vs Sx Rx
Weiss 1992[25]	US	VUR grade III, IV	< 10 yrs	4.5 yrs	No information	AbxP vs Sx Rx
BRSG 1983[26]	UK	VUR grade III or grade II with scarring	>1 yr	2 yrs	(+) UC	Sx Rx vs AbxP
Garcia-Aparicio 2013[27]	Spain	VUR grade II, III, IV	>1 yr	5 yrs	No information	Endo Rx vs Sx Rx
Capozza 2002[28]	Italy	VUR grade II, III, IV	>1 yr	1 yr	(+) UC	Endo Rx vs AbxP
Brandstrom 2011[29]	Sweden	VUR grade III, IV	1-2 yrs	2 yrs	Febrile UTI	Endo Rx vs AbxP vs no AbxP
Salih 2021[30]	Egypt	VUR grade III, IV	1- 10 yrs	2 yrs	No information	Endo Rx vs Sx Rx

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

Table (2) Results for pairwise comparisons of different treatment modalities

Outcomes	Treatment comparisons Treatment (1) vs (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 vs AbxP - [22-24]	50/238	63/235	0.75(0.43,1.29)
	Endo Rx vs AbxP -[28, 29]	20/105	10/90	2.03(0.89,4.64)
	AbxP vs No AbxP -[21, 25, 26]	26/152	24/145	1.07(0.51,2.24)
	Endo Rx vs Sx Rx -[27]	2/22	0/19	Not estimable
Progression of old lesions	AbxP vs Sx Rx - [20, 25, 26]	52/270	43/264	1.23(0.79,1.93)
	AbxP vs No AbxP -[24]	1/50	9/50	0.09(0.01,0.76)
Formation of new renal scars	AbxP vs Sx Rx - [20, 25]	33/223	36/215	0.86(0.51,1.44)
	AbxP vs No AbxP - [29]	0/69	9/68	Not estimable
	AbxP vs Endo Rx - [29]	0/69	6/66	Not estimable
	Endo Rx vs No Abxb - [29]	6/66	9/68	0.66(0.22,1.96)
RRU	Sx Rx vs Endo Rx - [27, 30]	77/80	66/80	5.02(1.47,17.13)
	Sx Rx vs AbxP - [26]	67/69	17/65	94.59(20.87,428.74)
	Endo Rx vs AbxP - [28]	40/52	10/30	8.33(3.14,22.13)

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

Table (3) Summary of findings of GRADE analysis for pairwise comparisons

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Control	With Intervention	Relative effect (95% CI)	Risk with Control	Risk difference with Intervention
UTI recurrence (AbxP vs No AbxP) (follow-up: range 1 years to 4 years)											
297 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	24/145 (16.6%)	26/152 (17.1%)	**OR 1.07** (0.51 to 2.24)	166 per 1,000	**10 more per 1,000** (from 74 fewer to 142 more)
UTI recurrence(Sx Rx vs AbxP) (follow-up: range 2 years to 5 years)											
473 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	63/235 (26.8%)	50/238 (21.0%)	**OR 0.75** (0.43 to 1.29)	268 per 1,000	**53 fewer per 1,000** (from 132 fewer to 53 more)
UTI recurrence(Endo Rx vs AbxP) (follow-up: range 1 years to 2 years)											
195 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	10/90 (11.1%)	20/105 (19.0%)	**OR 2.03** (0.89 to 4.64)	111 per 1,000	**91 more per 1,000** (from 11 fewer to 256 more)
UTI recurrence(Endo Rx vs Sx Rx) (follow-up: median 1 years)											
41 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	0/19 (0.0%)	2/22 (9.1%)	not estimable	0 per 1,000	

Table (3) Summary of findings of GRADE analysis for pairwise comparisons

Certainty assessment							Summary of findings				
Progression of old lesion(AbxP vs Sx Rx) (follow-up: range 2 to 5 years)											
534 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	43/264 (16.3%)	52/270 (19.3%)	**OR 1.23** (0.79 to 1.93)	163 per 1,000	**30 more per 1,000** (from 30 fewer to 110 more)
Progression of old lesion(AbxP vs No AbxP) (follow-up: median 4 years)											
100 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	9/50 (18.0%)	1/50 (2.0%)	**OR 0.09** (0.01 to 0.76)	180 per 1,000	**161 fewer per 1,000** (from 178 fewer to 37 fewer)
Formation of new renal scars(AbxP vs Sx Rx) (follow-up: range 4 to 5 years)											
438 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	36/215 (16.7%)	33/223 (14.8%)	**OR 0.86** (0.51 to 1.44)	167 per 1,000	**20 fewer per 1,000** (from 74 fewer to 57 more)
Formation of new renal scars(Endo Rx vs No AbxP) (follow-up: median 2 years)											
134 (1 RCT)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	9/68 (13.2%)	6/66 (9.1%)	**OR 0.66** (0.22 to 1.96)	132 per 1,000	**41 fewer per 1,000** (from 100 fewer to 98 more)
RRU(Sx Rx vs Endo Rx) (follow-up: range 2 to 5 years)											
160 (2 RCTs)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	66/80 (82.5%)	77/80 (96.3%)	**OR 5.02** (1.47 to 17.13)	825 per 1,000	**134 more per 1,000** (from 49 more to 163 more)

Table (3) Summary of findings of GRADE analysis for pairwise comparisons

Certainty assessment							Summary of findings				
RRU(Sx Rx vs AbxP) (follow-up: median 2 years)											
134 (1 RCT)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	17/65 (26.2%)	67/69 (97.1%)	**OR 94.59** (20.87 to 428.74)	262 per 1,000	**709 more per 1,000** (from 619 more to 732 more)
RRU(Endo Rx vs AbxP) (follow-up: median 1 years)											
82 (1 RCT)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	10/30 (33.3%)	40/52 (76.9%)	**OR 8.33** (3.14 to 22.13)	333 per 1,000	**473 more per 1,000** (from 278 more to 584 more)

CI: confidence interval; **OR:** odds ratio

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.

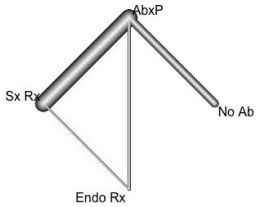
Explanations

a. Unclear explanation of randomization process in two studies and some missing data in one study
b. Unclear explanation of randomization process

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

Patient or population: VUR Grade II-IV
Setting: Various treatment modalities in children with VUR Grade II-IV
Interventions: Surgical treatment, Endoscopic treatment, 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[a]	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 treatmen (No AbxP)	**0.15** (-0.45 to 0.75)	⨁⨁⨁⨁ High	0.31	Probably inferior

NMA-SoF table definitions

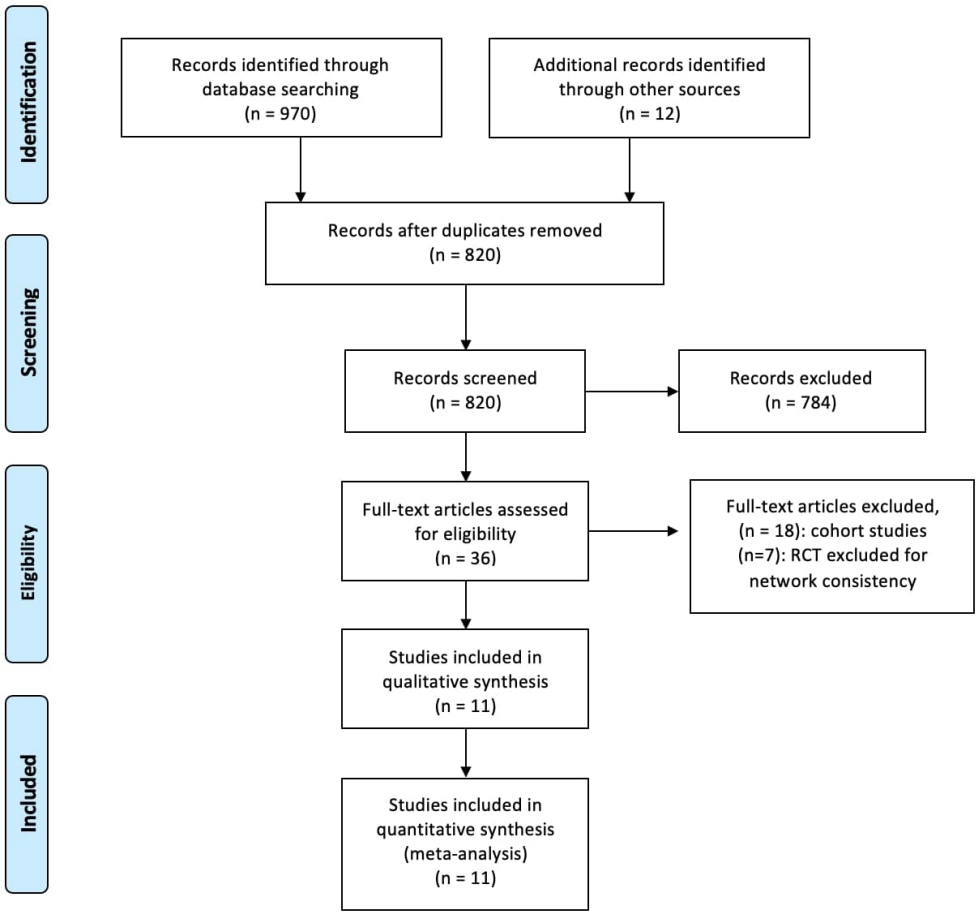
*Lines represent direct comparisons

**Network estimate effects are reported as Log OR and the results are expressed in 95% confident interval since the frequentist model has been conducted.

***Ranking is calculated by P-score by netrank function

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.

Explanations
a. Unclear explanation of randomization process in two studies and some missing data in one study



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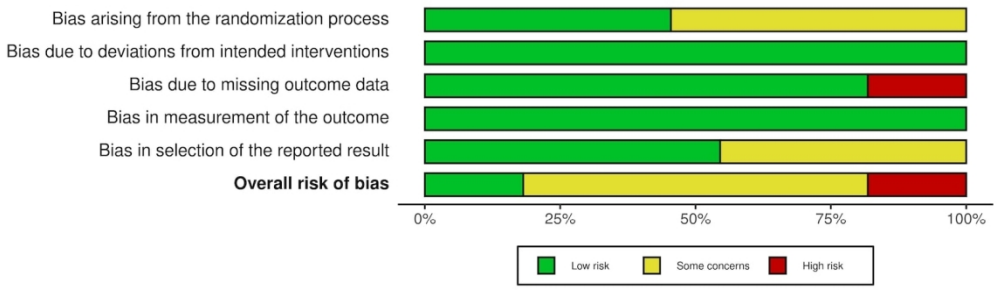

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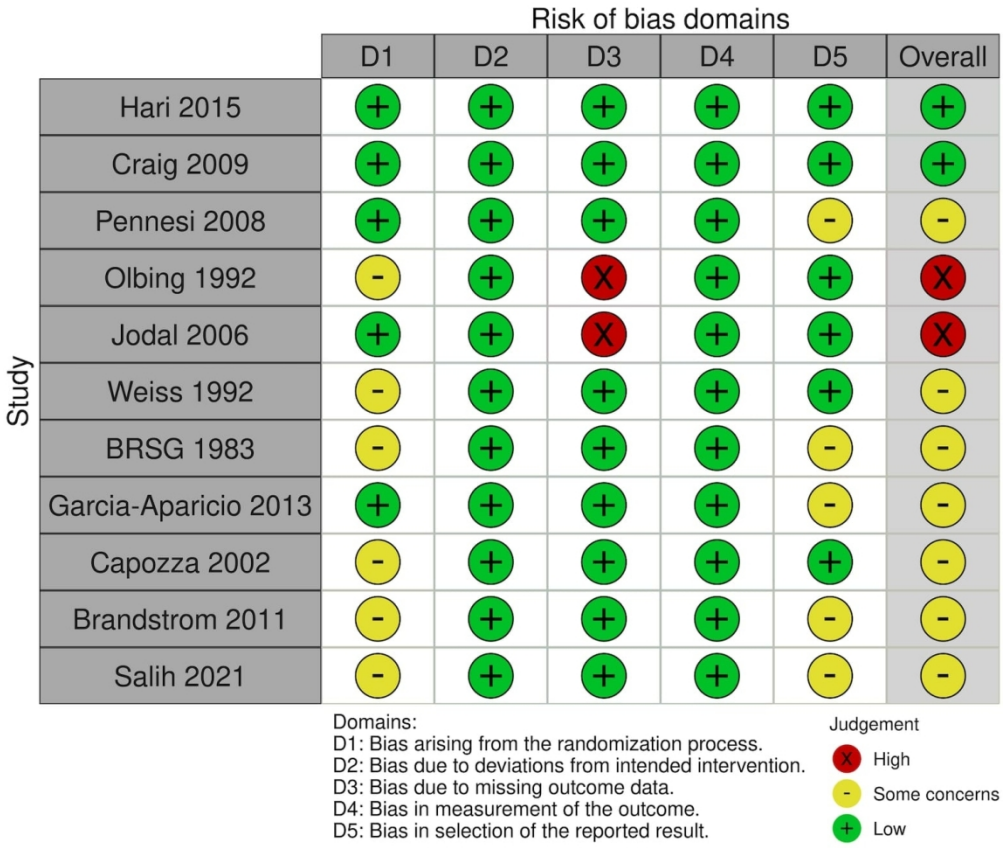

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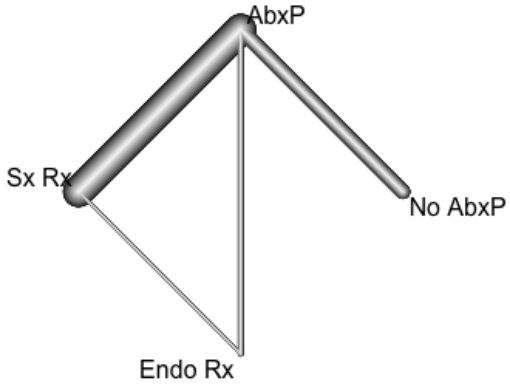

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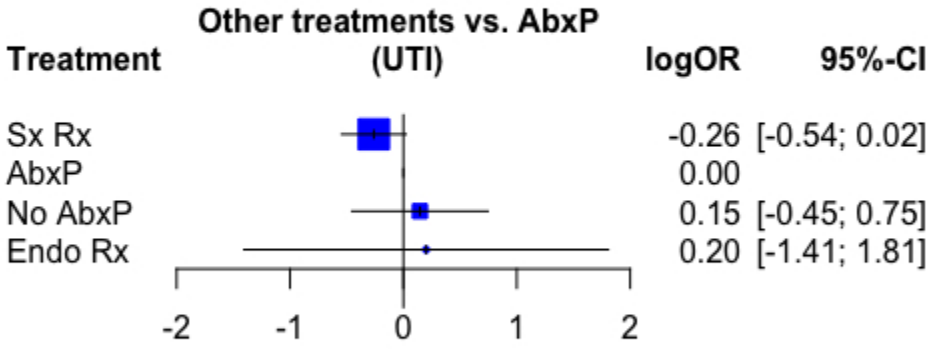

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Effectiveness of Various Treatment Modalities in Children with Vesicoureteral Reflux Grade II to IV: A Systematic Review and Network Meta-analysis

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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 randomized control trials were included in this study. Effectiveness of treatment modalities were 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 Grade II-IV.

These findings may offer a better understanding of each treatment and evidence-based suggestions for the choice of treatment, which should be individualized 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.

What this study adds

There is no significant difference in 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 individualized 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 to

3%.[2] However, in those with UTI combined with VUR, the incidence rises to 30 to 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 (VCUG) 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, nonoperative 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 grade (I, II) and high grade (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 randomized 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 standardized. Therefore, most randomized control 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, III, and 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 (vesicoureteral reflux; vesicoureteral reimplantation; endoscopic treatment or antibiotic prophylaxis). 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 Involving a Network Meta-Analysis (PRISMA-NMA) statement. The number of included and excluded studies were 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, antibiotic prophylaxis, or surveillance with no antibiotic prophylaxis) 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.L. Chang and C.H. Chen) extracted the data from each eligible study, including urinary tract infection (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.K Hsu, Stephen S.D. Yang and S.J. Chang) 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 urinary tract infection (UTI) according to the criteria defined by each study between treatment modalities.

Secondary outcomes were the rate of worsening of previous renal scars (i.e. 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 Revman 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 odds ratios (ORs) for pairwise comparisons and odds ratios in logarithmic scale (log ORs) for comparisons in network meta-analysis. Random-effects 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 were accessed with the methods provided in GRADE 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 to IV. The main target audience includes pediatricians, 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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 Fig 1. All 11 studies were randomized control trials 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 summarized in Table (1).

Risk of bias

Nearly half of the included studies reported unclear information about randomization, 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 summarized in Fig 2 (a) 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 (Fig 3) including a total of 9 studies. Our model showed two strong arms (AbxP vs no AbxP and AbxP vs Sx Rx) each including 3 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 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 analyzed with primary outcomes (urinary tract infection) simultaneously measured by network meta-analysis. Other outcomes such as renal scarring and resolution by renal units were only analyzed 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 Fig (4). However, the mixed comparison results were not significant with low heterogeneity.

Progression of old lesions

A total of 4 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 (RRU)

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 2 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 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 hematuria (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 randomization process and outcome data. Overall certainty of the evidence and summary of findings table for pairwise comparison was 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 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 includes 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 RIVUR trial[33] supported using AbxP because of its significant reduction in UTI recurrence, but PRIVENT 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 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 intra- and extravesical reimplantation technique are most commonly used methods.[35] Sx Rx included in our study are open ureteral reimplantation methods, mostly Cohen and Politano-Leadbetter technique. Despite a significant better resolution by renal units 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 (STING) 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 (Dx/HA) 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 randomized 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 Grade II-IV. These findings could offer valuable evidence-based insights for guiding treatment

selection, emphasizing the importance of individualized approaches based on each patient's specific risk factors.

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Author Contributions Statement

C.L Chang and C.H Chen conceptualized and designed the study, performed data collection, data analysis and drafted the original manuscript. S.D Yang, C.K Hsu and S.J. Chang coordinated and supervised data collection, and critically reviewed the manuscript. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Legends to The Figures

Fig. 1 Research flow chart

Fig. 2(a) Risk of bias graph: each risk of bias component displayed as percentage across papers

Fig. 2(b) Risk of bias summary: each risk of bias component for each paper

Fig. 3 Network graph of each treatment for UTI

Fig. 4 Comparison of UTI recurrence after each treatment of VUR

Table 1 Study characteristics of included studies

Table 2 Results for pairwise comparisons of different treatment modalities

Table 3 Summary of findings of GRADE analysis for pairwise comparisons

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

Declarations

Ethics approval

This is a systematic review and network meta-analysis study. The Research Ethics Committee has confirmed that no ethical approval is required and there is no clinical trial registration.

Conflict of interest

None.

Data availability statement

Data are available on reasonable request.

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 yrs	1 yr	(+) UC	AbxP vs no AbxP
Craig 2009[21]	Australia	VUR grade III, IV	<18 yrs	1 yrs	(+) UC	AbxP vs no AbxP
Pennesi 2008[22]	Italy	VUR grade II, III, IV	<2.5 yrs	4 yrs	Febrile UTI	AbxP vs no AbxP
Olbing 1992[18]	Germany	VUR grade III, IV	<11 yrs	5 yrs	No information	AbxP vs Sx Rx
Jodal 2006[19]	US	VUR grade III, IV	<11 yrs	5 yrs	(+) UC	AbxP vs Sx Rx
Weiss 1992[23]	US	VUR grade III, IV	< 10 yrs	4.5 yrs	No information	AbxP vs Sx Rx
BRSG 1983[24]	UK	VUR grade III or grade II with scarring	>1 yr	2 yrs	(+) UC	Sx Rx vs AbxP
Garcia-Aparicio 2013[25]	Spain	VUR grade II, III, IV	>1 yr	5 yrs	No information	Endo Rx vs Sx Rx
Capozza 2002[26]	Italy	VUR grade II, III, IV	>1 yr	1 yr	(+) UC	Endo Rx vs AbxP
Brandstrom 2011[27]	Sweden	VUR grade III, IV	1-2 yrs	2 yrs	Febrile UTI	Endo Rx vs AbxP vs no AbxP
Salih 2021[28]	Egypt	VUR grade III, IV	1- 10 yrs	2 yrs	No information	Endo Rx vs Sx Rx

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

Table (2) Results for pairwise comparisons of different treatment modalities

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

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

Table (3) Summary of findings of GRADE analysis for pairwise comparisons

Outcomes	№ 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 years to 4 years	297 (3 RCTs)	⊕⊕⊕⊕ High	**OR 1.07** (0.51 to 2.24)	166 per 1,000	**10 more per 1,000** (74 fewer to 142 more)
UTI recurrence (Sx Rx vs AbxP) follow-up: range 2 years to 5 years	473 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	**OR 0.75** (0.43 to 1.29)	268 per 1,000	**53 fewer per 1,000** (132 fewer to 53 more)
UTI recurrence (Endo Rx vs AbxP) follow-up: range 1 years to 2 years	195 (2 RCTs)	⊕⊕⊕⊕ High	**OR 2.03** (0.89 to 4.64)	111 per 1,000	**91 more per 1,000** (11 fewer to 256 more)
UTI recurrence (Endo Rx vs Sx Rx) follow-up: median 1 years	41 (1 RCT)	⊕⊕⊕⊕ High	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Progression of old lesion (AbxP vs Sx Rx) follow-up: range 2 to 5 years	534 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	**OR 1.23** (0.79 to 1.93)	163 per 1,000	**30 more per 1,000** (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 1,000	**161 fewer per 1,000** (178 fewer to 37 fewer)
Formation of new renal scars (AbxP vs Sx Rx) follow-up: range 4 to 5 years	438 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	**OR 0.86** (0.51 to 1.44)	167 per 1,000	**20 fewer per 1,000** (74 fewer to 57 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Intervention
Formation of new renal scars (Endo Rx vs No AbxP) follow-up: median 2 years	134 (1 RCT)	⊕⊕⊕◯ Moderate[b]	**OR 0.66** (0.22 to 1.96)	132 per 1,000	**41 fewer per 1,000** (100 fewer to 98 more)
RRU (Sx Rx vs Endo Rx) follow-up: range 2 to 5 years	160 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	**OR 5.02** (1.47 to 17.13)	825 per 1,000	**134 more per 1,000** (49 more to 163 more)
RRU (Sx Rx vs AbxP) follow-up: median 2 years	134 (1 RCT)	⊕⊕⊕◯ Moderate[b]	**OR 94.59** (20.87 to 428.74)	262 per 1,000	**709 more per 1,000** (619 more to 732 more)
RRU (Endo Rx vs AbxP) follow-up: median 1 years	82 (1 RCT)	⊕⊕⊕◯ Moderate[b]	**OR 8.33** (3.14 to 22.13)	333 per 1,000	**473 more per 1,000** (278 more to 584 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

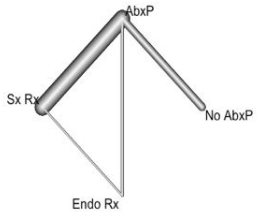
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is 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.

Explanations

a. Unclear explanation of randomization process in two studies and some missing data in one study
b. Unclear explanation of randomization process

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

Patient or population: VUR Grade 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[a]	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

NMA-SoF table definitions

*Lines represent direct comparisons

**Network estimate effects are reported as Log OR and the results are expressed in 95% confident interval since the frequentist model has been conducted.

***Ranking is calculated by P-score by netrank function

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.

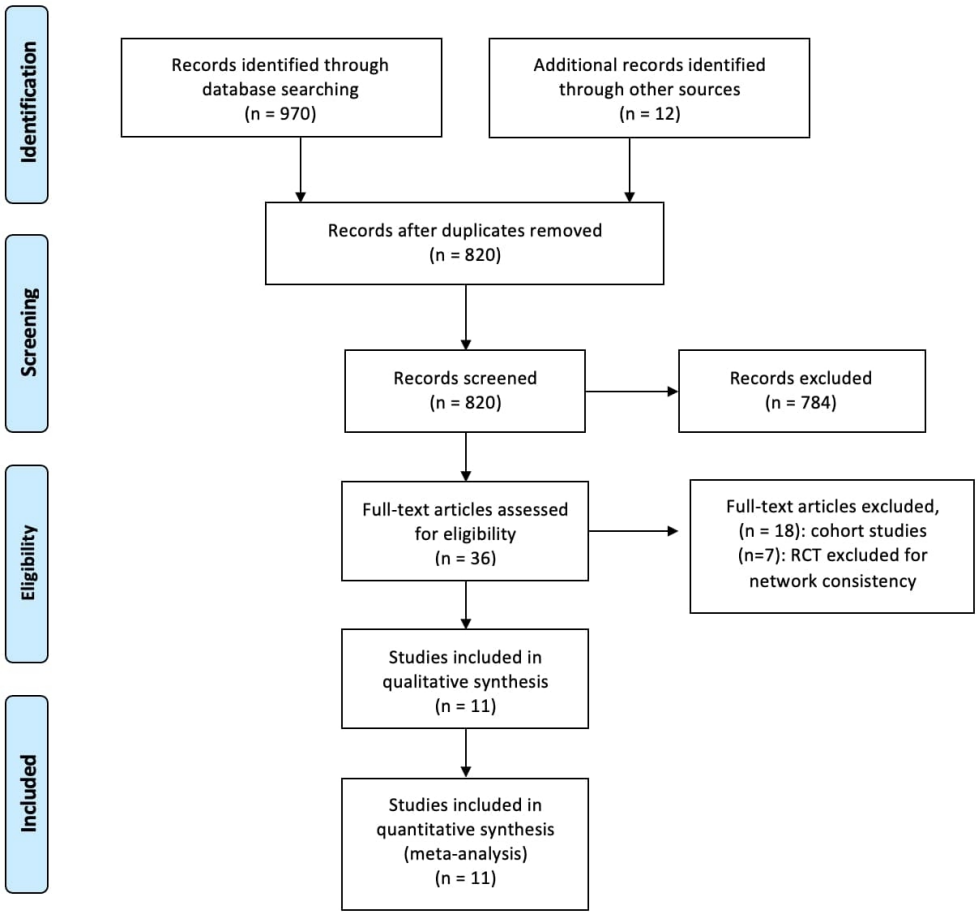
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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.

Explanation

a. Unclear explanation of randomization process in two studies and some missing data in one study



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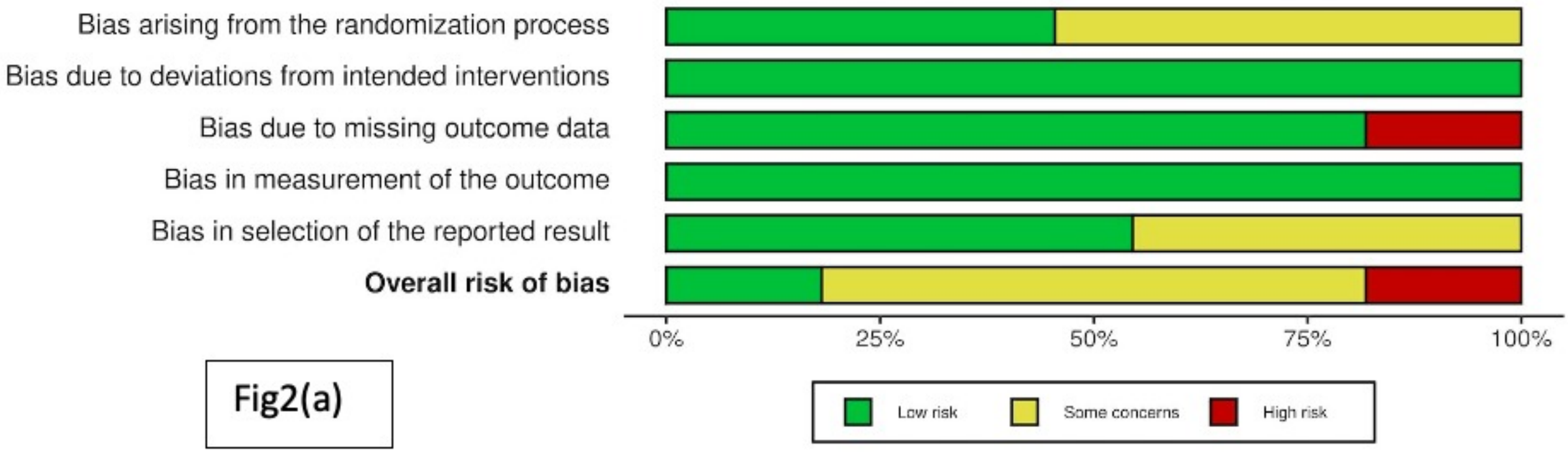


Fig2(a)

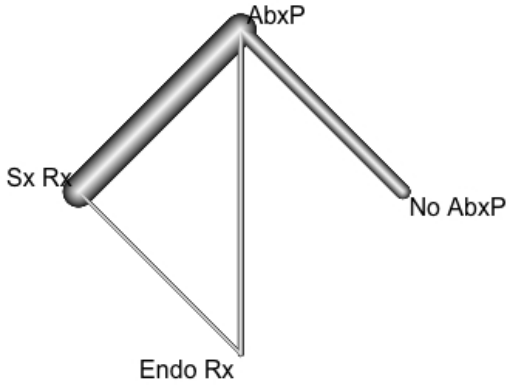
Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Hari 2015	+	+	+	+	+	+
Craig 2009	+	+	+	+	+	+
Pennesi 2008	+	+	+	+	-	-
Olbing 1992	-	+	X	+	+	X
Jodal 2006	+	+	X	+	+	X
Weiss 1992	-	+	+	+	+	-
BRSG 1983	-	+	+	+	-	-
Garcia-Aparicio 2013	+	+	+	+	-	-
Capozza 2002	-	+	+	+	+	-
Brandstrom 2011	-	+	+	+	-	-
Salih 2021	-	+	+	+	-	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

Fig2(b)



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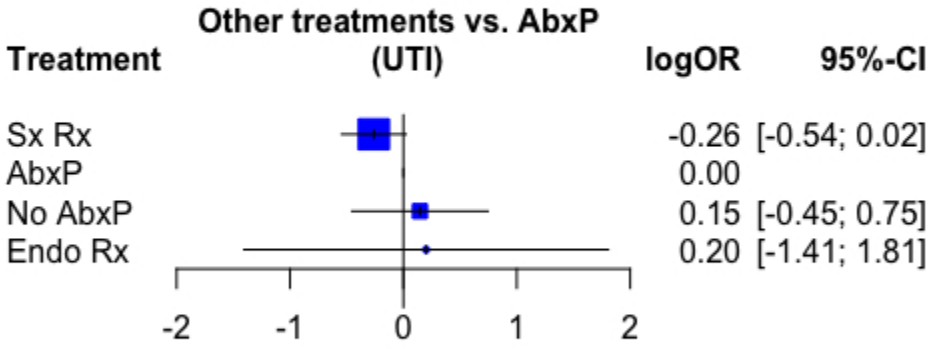

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