Interventions for Primary Vesicoureteric Reflux

Filipa Jalles[1], Ricardo M Fernandes[2,3,4], Marta Janeiro[1], José Gonçalo Marques[5], Rosário Stone[6], Miroslava Gonçalves[1]

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Introduction

Primary vesicoureteric reflux (VUR), or the retrograde flow of urine from the bladder to the ureter and kidney during voiding is an anatomical and functional defect of the vesicoureteric junction. It is a risk factor for urinary tract infections (UTI) detected in 30%-50% of children with recurrent UTI and in 10%-20% of patients with antenatal detected hydronephrosis.[1,2] It may lead to permanent parenchymal damage post-UTI with renal involvement in 10%-40% of patients,[3-5] but parenchymal loss may also be due to congenital dysplasia. The long-term adverse outcomes of renal scarring are hypertension and end-stage renal disease found in 10%-20% of children with reflux nephropathy.[2,4] In the past, a full evaluation of VUR to prevent long-term adverse effects was recommended. However, end-stage renal disease caused by reflux nephropathy is extremely rare, and most end-stage renal disease patients have congenital reflux nephropathy distinct from acquired renal parenchymal post-febrile urinary tract infection events.[6-8]

A range of severity exists, as a spontaneous resolution may occur depending on the initial grade of reflux and the interplay of numerous factors.[2] The currently available treatment options include long-term low-dose antibiotics, surgical reimplantation of the ureters, endoscopic correction, complementary medicines, circumcision, oxybutynin, or a combination of interventions.[3] There has been persisting controversy regarding the optimal management strategy and the most effective timing of treatment as well as considerable variability in clinical practice worldwide.[2-5,9]

Aim

This Cochrane Corner presents and discusses the results of a 2019 Cochrane review that aimed to evaluate the evidence for both benefits and harms of the currently available treatment options for primary vesicoureteric reflux: operative, non-operative, or no intervention. This was an update of a review first published in 2004 and updated in 2007 and 2011.

Methods

A systematic review was conducted by searching the Cochrane Kidney and Transplant Specialized Register up to May 2018, with studies identified from CENTRAL, MEDLINE, EMBASE, trial registries, hand searching of journals and conference proceedings, and other sources of unpublished or incomplete studies.

The authors included all randomized controlled trials reported in any language, which included male and female participants of any age with a diagnosis of primary vesicoureteric reflux by voiding cystourethrogram, with or without urinary tract infections. Patients with vesicoureteric reflux associated with other urological abnormalities were excluded. The interventions of interest were surgery (open and endoscopic techniques), antibiotic prophylaxis of any duration, circumcision, non-invasive treatments, complementary medicines, and any combination of therapies. The primary outcome was the number of patients with symptomatic urinary tract infections, including febrile urinary tract infections. The secondary outcomes were the number of patients:

- With febrile urinary tract infections;
- with at least one repeat positive urine culture during follow-up;

1. Pediatric Surgery Unit, Pediatrics Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal
2. Pediatrics Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal
3. Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Lisbon Academic Medical Centre, Lisbon, Portugal
4. Portuguese Collaborating Centre of the Iberoamerican Cochrane Network, Cochrane Portugal, Lisbon, Portugal
5. Pediatric Infectious Diseases Unit, Pediatrics Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal
6. Nephrology and Renal Transplant Unit, Pediatrics Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon Academic edical Centre, Lisbon, Portugal
8. Pediatric Surgery Unit, Pediatrics Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal
Corresponding Author
Filipa Jalles
https://orcid.org/0000-0002-6474-4717
fjalles@gmail.com
Pediatric Surgery Unit, Pediatrics Department, Hospital de Santa Maria, Avenida Professor Egas Moniz, 1649-035 Lisboa, Portugal
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- With renal parenchymal abnormality, whether new, progression from pre-existing damage, resolution or end-stage renal disease, and diagnosed by ultrasound, intravenous pyelography, or technetium 99m labeled dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy);
- Previously unaffected patients who developed hypertension;
- With kidney function impairment;
- Number of children and/or ureters without vesicoureteric reflux on follow-up voiding cystourethrogram, microbial resistance, obstruction following the correction of vesicoureteric reflux, or any reported drug- or surgery-related adverse events.

Two authors independently determined the study eligibility, assessed the quality, and extracted and compiled the data. The risk of bias in the included trials was assessed using the Cochrane Risk of Bias Tool (2008). Different measures of the treatment effect were used according to the type of outcomes, namely the risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous variables. The measurements of the effect were presented with 95% confidence intervals (CI). The meta-analysis used the random effects model, with subsequent testing for robustness by applying the fixed effect model. Statistical heterogeneity between the studies and in the subgroup analysis was assessed using Cochrane's Q statistic and I^2. A formal evaluation of the different sources of heterogeneity was not possible due to an insufficient number of studies within each comparison group. The quality of the evidence that was related to each of the main outcomes was evaluated using GRADE.

Results

A total of 34 randomized controlled trials were included, involving 4,001 participants. The most frequent comparisons were long-term low-dose antibiotics *versus* no treatment (eight studies) or placebo (four studies) and antibiotics *versus* the surgical reimplantation of ureters plus antibiotics (seven studies). Other tested treatments included endoscopic correction (four studies), different materials for endoscopic injection (four studies), and surgical reimplantation, circumcision, probiotics, cranberry product, and oxybutynin (one study each). Only four studies were considered as having a low risk of bias across all the domains. Table 1 summarizes the results for the primary outcome and selected secondary outcomes across the main comparisons. The results for primary and most secondary outcomes only included data from children.

Long-term low dose antibiotic prophylaxis did not significantly reduce the risk of repeat symptomatic urinary tract infections or febrile urinary tract infections at one to two years of follow-up compared with no treatment or placebo, nor the number of children with renal abnormalities on a DMSA scan (Table 1). It also may make little or no difference in the development of renal abnormalities (eight studies, n = 1503, RR 0.73, 95% CI 0.33 to 1.61) or the deterioration of the existing ones (three studies, n = 446, RR 0.68, 95% CI 0.27 to 1.73). No significant difference in the follow-up positive urine cultures was found. The reported adverse effects showed little or no difference between the groups, but antibiotic prophylaxis increased the risk of bacterial resistance in repeat symptomatic urinary tract infections (six studies, RR 2.72, 95% CI 1.85 to 4.00).

Ureteric reimplantation by open surgery (using different surgical methods) plus antibiotic prophylaxis was compared to low-dose antibiotic prophylaxis alone, with two studies reporting on febrile urinary tract infections favoring the surgical group, but with one study finding no difference in any symptomatic urinary tract infections (Table 1). There was no difference in repeat positive urine cultures as well as the new or progression of renal parenchymal abnormality by intravenous pyelography (IVP) or DMSA scan. Three studies reported on end-stage renal disease and hypertension, with no difference but imprecise results. The data on the resolution of vesicoureteric reflux was not combined due to the differences in reporting and missing data. Adverse events were generally not well reported; one study found 7% postoperative obstruction, and six other post-operative events were described in another study.

Four studies compared the endoscopic injection combined with or without antibiotics to antibiotic prophylaxis with no significant difference in febrile urinary tract infections (Table 1). There was little or no difference in new or deteriorating renal damage on DMSA scan, but full resolution of vesicoureteric reflux and improvement in vesicoureteric reflux grade favored the endoscopic treatment group, with low certainty evidence. When compared to no treatment, a single study found a reduced risk of symptomatic and febrile urinary tract infections in the endoscopic treatment group (n = 133, RR 0.55, 95% CI 0.33 to 0.94). However, no difference was found regarding the renal parenchymal defects, and end-stage renal disease and hypertension were not reported. Different materials for endoscopic subureteric injections were tested, with differences reported in some secondary outcomes. The one study comparing surgical reimplantation with endoscopic injection found no differences in primary and secondary outcomes.

Table 1. Summary of findings for the primary outcome and selected secondary outcomes in the main comparisons

Outcomes	Participants, n (studies)	Relative effect, risk ratio (95% CI)	Certainty of evidence (GRADE)
Antibiotic prophylaxis *versus* placebo or no treatment			
Symptomatic UTI by 1 to 2 years			
All trials	1,667 (9)	0.77 (0.54 to 1.09)	Low
Low risk of bias trials	943 (3)	0.85 (0.40 to 1.79)	Moderate
Febrile UTI by 1 to 2 years	1,667 (9)	0.83 (0.56 to 1.21)	Low
New and progressive abnormalities on ^{99m}Tc-DMSA scan by 1-3 years	1,288 (7)	0.83 (0.42 to 1.62)	Low
Surgical reimplantation of ureters plus antibiotics *versus* antibiotics alone			
Symptomatic UTI by 4 to 5 years	297 (1)	0.95 (0.67 to 1.35)	Moderate
Febrile UTI by 5 years	429 (2)	0.43 (0.27 to 0.70)	Moderate
New and progressive abnormalities on IVP at 4-5 years	468 (3)	1.05 (0.85 to 1.29)	Moderate
Endoscopic injection treatment *versus* antibiotics alone			
Symptomatic UTI by 1 to 2 years	254 (3)	0.80 (0.37 to 1.75)	Low
Febrile UTI by 1 to 2 years	254 (3)	0.74 (0.31 to 1.78)	Low
New and progressive abnormalities on 99mTc-DMSA scan by 1-2 years	208 (2)	1.20 (0.36 to 3.96)	Low

CI - confidence interval; RR - risk ratio; UTI - urinary tract infection; IVP - intravenous pyelography; ^{99m}Tc-DMSA - technetium 99m labeled dimercaptosuccinic acid scintigraphy.

Two studies (n = 248) compared probiotics with antibiotic prophylaxis and showed no difference in the risk of repeat symptomatic urinary tract infections (RR 0.82, 95% CI 0.56 to 1.21), febrile urinary tract infections, and renal parenchymal defects on DMSA scan. *Escherichia coli* resistance was higher with antibiotics (RR 0.38, 95% CI 0.21 to 0.69).

All other comparisons were based on individual studies with very low certainty of evidence.

Conclusion

The authors of this review concluded that the use of long-term low-dose antibiotics may make little or no difference in repeat symptomatic and febrile urinary tract infections in children with vesicoureteric reflux when compared with no treatment with low certainty evidence. Small studies of variable methodological quality and unexplained heterogeneity make drawing firm conclusions challenging. The adverse effects were minor and infrequent but poorly reported, and a threefold increase in prophylactic drug resistance in subsequent urinary tract infections was described. The added benefit of surgery and endoscopic correction of vesicoureteric reflux over long-term low-dose antibiotic use remains uncertain. The benefit found in surgery regarding repeat febrile urinary tract infections may be overestimated and no evidence was found to validate any long-term effect in keeping the infection from spreading to the upper tract. Informed decision making must also consider the risk of adverse events associated with these interventions. Evidence is insufficient to support or deny the role of complementary therapies, circumcision, and oxybutynin in preventing urinary tract infections in children with vesicoureteric reflux.

Comments

Evidence on the benefits and harm of diagnosing and treating children with vesicoureteric reflux has been historically limited by the absence of trials including placebo or no treatment arms. The results from recently concluded studies with these comparators are included in this review. However, some limitations to this body of evidence must be considered. Effect estimates were imprecise and there was heterogeneity in the definition of outcomes and successful treatment. Differences in the baseline characteristics were not explored, but factors such as lower urinary tract dysfunction and grade of vesicoureteric reflux may influence the treatment effects and limit the generalizability of these results. High-quality studies are particularly needed to evaluate the added benefit of surgical correction over conservative treatment, considering both recurrent urinary tract infections but also long-term measures of renal function, since no firm conclusions could be taken from this review.

The clinician is left with the need to make individual judgments, as explicit guidance is not available for different sub-groups of children, and broad

recommendations should be viewed with caution. Additional evidence from observational studies with long-term follow-up is useful. A systematic review concluded that children without structural kidney abnormalities after the first febrile urinary tract infection are not at significant risk of developing urinary tract infections-related end-stage renal disease.[10] In Portugal, the majority of pediatric centers follow the European Society of Pediatric Urology recommendations,[2] although practices vary between conservative and surgical approaches based on patients' individual factors and center preferences. Moving forward, clear and consistently applied protocols at the center level, based on similar baseline identification of risk and follow-up evaluation, would generate valuable data to evaluate the comparative effectiveness and safety of different treatment approaches for primary vesicoureteric reflux.

Keywords: Child; Randomized Controlled Trials as a Topic; Risk Factors; Urinary Tract Infections/etiology; Urinary Tract Infections/prevention & control; Vesico-Ureteral Reflux/complications; Vesico-Ureteral Reflux/therapy; Vesico-Ureteral Reflux/surgery

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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