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Assessment of secondary surgical repair versus salvage endoscopic correction for persistent (recurrent) vesicoureteral reflux in children: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Developing a comprehensive understanding of the current estimates for incidence and prevalence of persistent vesicoureteral reflux (VUR) following ureteroneocystostomy or endoscopic correction is crucial. This knowledge will enable us to develop strategies for shared decision-making. Furthermore, a thorough examination of the available evidence will provide an opportunity to formulate evidence-based policies aimed at preventing VUR persistence.

Methods and analysis A systematic review and meta-analysis on the success rate and safety of secondary surgical repair versus salvage endoscopic correction for persistent (recurrent) VUR after failed cases in children will be conducted. The following international electronic databases will be searched: MEDLINE, Embase and The Cochrane Library (from inception to February 2025). For unpublished and ongoing studies, international experts in the field of research will be contacted. There will be no language restrictions; where possible, we will translate literature in languages other than English and report any literature we are unable to translate. The methodological quality of interventional studies (the risk of bias) will be independently assessed in individual studies using the Cochrane Risk of Bias tool 2, and observational studies by The Effective Public Health Practice Project critical appraisal tool. The meta-analyses will be performed using Comprehensive Meta-Analysis, V.4. The current protocol adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocol 2015 guidelines, thereby upholding the highest methodological standards.

Ethics and dissemination Ethical approval is not required. The outcomes of this systematic review will be presented in conference presentations and published in peer-reviewed journals.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A minimum of two to three reviewers will select, extract and assess the quality of studies, which will minimise the likelihood of bias affecting the results.
⇒ An analysis of the resolution rate and the occurrence, prevalence and risk factors of recurrent vesicoureteral reflux in children will enhance the completeness and certainty of a body of evidence.
⇒ There is a possibility that a language bias may exist due to the inability to search medical databases in other languages due to language barriers.
⇒ Heterogeneity of included studies and sample size issues may affect the pooling of data and the ability to conduct a meta-analysis.

BACKGROUND

Vesicoureteral reflux (VUR) is a condition characterised by backflow of urine from the bladder to the ureters and kidneys. Its prevalence among healthy paediatric populations is estimated to be between 0.4% and 1.8%,[1] while among patients with febrile urinary tract infections (UTIs), it is estimated to be between 30% and 50%.[2] Treatment options for VUR include antibiotic prophylaxis, endoscopic correction and ureteroneocystostomy (UNC). If left untreated, VUR can lead to UTIs, renal scarring,[3] hypertension[4] and ultimately chronic kidney disease.[5]

Indications for the treatment of persistent VUR include recurrent UTIs, persistent VUR and new renal scars. Depending on the initial operative method performed, persistent VUR may develop: 7.5% of reimplantation cases require reoperation,[6 7] while 10-20% of endoscopic correction cases of higher grade VUR (≥grade III) will require more than one injection.[8 9] In 80% of persistent cases after UNC, low-grade VUR resolves spontaneously during the first postoperative year.[10]

Persistent VUR following UNC can be treated by (1) watchful waiting without antibiotic prophylaxis; (2) antibiotic prophylaxis;

(3) a second attempt of reimplantation; (4) endoscopic injection. The decision on which type of treatment option will be chosen depends on laterality, grade of persistent VUR, patient's age, number of operations performed and presence of UTI. Multiple factors play a role in the persistence of VUR after UNC:[11] creation of short submucosal tunnel; unstable bladder (reimplantation into non-compliant, not-fully-completing bladder); aperistaltic distal ureter due to chronic inflammatory or ischaemic changes from previous operations. Consequently, repeat surgeries following UNC have drawbacks in terms of technical implementation: they always take longer operative time than primary operations due to the difficulty in dissection and mobilisation of fibrotic and adhesive structures (difficult surgical planes). Subsequently, redo surgeries hold less eventual success rate and may result in the preservation of complications.

Similarly, recurrence of VUR after endoscopic correction may be managed by the options listed above for the UNC cases. There are several points to highlight in the preservation of VUR after endoscopic correction:[12] grade of VUR; location and configuration of ureteral orifice; presence of hyperactive bladder; presence of UTI/inflammation before injection; properties of the injectable material; surgeon's experience; implementation of injection technique correctly. Although the success rate of endoscopic injection is significantly lower than UNC, it has a number of advantages: less postoperative pain, bladder spasms; no surgical scars; short procedure time; short time to discharge; minimal use of postoperative analgesics; ability to repeat the procedure.

We intend to carry out a comprehensive review to gather, evaluate and integrate all existing evidence on the recurrent VUR following UNC or endoscopic correction to identify the radiological and clinical resolution rates and safety of these secondary redo surgeries. Specifically, by combining all relevant published information, this systematic review aims to furnish dependable and present-day estimates of the occurrence, prevalence and risk factors for persistent VUR. The emphasis on the formative years of childhood is to pinpoint early prevalent factors that may prove useful in the long run for devising evidence-based policies for interventions at an early stage.

METHODS AND ANALYSIS

Types of studies

All interventional (randomised control trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), etc), and observational studies (cohort, case-control, cross-sectional etc) on the success rates and cost-effectiveness of secondary ureteral reimplantation (open, laparoscopic and robotic-assisted) versus salvage endoscopic correction of paediatric VUR will be included. Reviews, studies in abstract form, case series, case reports and animal studies will be excluded.

Participants

Children, up to 18 years of age with recurrent VUR who had either ureteral reimplantation (open, laparoscopic, pneumovesicoscopic and robotic) or endoscopic correction will be included.

Outcome measures

Primary outcomes: Our primary outcome will include radiological and clinical resolution rate of the persistent VUR after the redo cases following the unsuccessful endoscopic correction and/or ureteral reimplantation.

Secondary outcomes: Secondary outcomes will include average surgery time, hospital discharges and average length of stay, and cost effectiveness of the performed salvage surgery.

Search strategy

The following international electronic databases will be searched systematically by two authors (KE, ZA): MEDLINE, Embase and The Cochrane Library (from inception to February 2025). Additional references will be located by searching the references cited in identified papers, as well as searching databases of the proceedings of international conferences, such as ISI Conference Proceedings Citation Index and ZETOC (British Library). We have consulted a methodologist on optimising our search strategy, and the following keywords will be used for literature search: (recurrent OR subsequent operation OR redo OR reoperation OR secondary OR salvage OR following OR persistent VUR OR failed previous antireflux surgery OR rescue) AND ((ureteric reimplantation OR ureteral reimplantation OR vesicoureteral reimplantation OR ureteroneocystostomy OR ureteroneocystostomy OR UNC OR UR) OR (endoscopic injection OR suburetteral injection OR endoscopic reinjection OR attempted VUR correction OR complex VUR OR tissue-augmenting substance OR endoscopic correction OR bulking agent injection)). The full search strategy is provided in the online supplemental materials (Search strategies 1 and 2). For unpublished and ongoing studies, international experts in the field of research will be contacted. There will be no language restrictions; where possible, we will translate literature in languages other than English and report any literature we are unable to translate.

Search terms will be developed using medical subject headings and text words related to secondary surgical repair versus salvage endoscopic correction for persistent reflux after failed antireflux treatment. After finalisation of the MEDLINE search strategy criteria, the latter will be adapted for the remaining electronic databases.

Study screening

Two reviewers (KK, DK) will screen titles and abstracts of the retrieved articles independently; any discrepancies will be resolved by consensus and a third reviewer (KE) will arbitrate disagreements. Full text copies of potentially relevant studies will be obtained and their eligibility for inclusion independently assessed by two reviewers (AS,

SE); discrepancies will be resolved by consensus and disagreements will be arbitrated by a third reviewer (KE).

Data extraction and reporting

Two reviewers (AS, ZA) will independently extract relevant information and study data onto a customised data extraction sheet. Any discrepancies in data extraction will be resolved by discussion or arbitration by a third reviewer (UN) if agreement cannot be reached. Descriptive tables will be used to summarise retrieved literature and characteristics of included studies contributing to the overall evidence.

The following data will be extracted from included studies: study design, country, period, successful outcome definition, participant information (number, age, VUR grade, follow-up time and group matched characteristics), surgery-related information (surgery time, estimated blood loss and intraoperative complications) and data of relevant outcomes (length of hospital stay, success rate, postoperative complications, postoperative urine derivation, postoperative analgesia usage and hospital cost). The mean and SDs of relevant continuous data will be extracted, and event and total numbers of related classified data will also be collected. When needed, we will contact the original authors for complete data. This systematic review will be reported according to guidance from the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[13]

Quality assessment and analysis

Two reviewers (ZA, KE) will independently undertake the quality and the potential for risk of bias of eligible interventional studies by using the Cochrane Risk of Bias 2 tool.[14]

The methodological quality of observational studies will be assessed according to the Effective Public Health Practice Project tool. We will also derive component-specific (ie, suitability of the study design for the research question; risk of selection bias; exposure measurement; outcome assessment; and generalisability of findings) and overall grading for each observational study.[15] Any discrepancies will be resolved by discussion or arbitration by a third reviewer (AR) in the event of any disagreement.

Data synthesis

Each step of the data synthesis process will be completed by two reviewers (KE, UN). Narrative synthesis of the data will be undertaken. In addition, for studies deemed to be reasonably clinically, methodologically and statistically homogeneous, meta-analyses using random-effects models will be performed. In comparison to fixed-effect meta-analysis, the random-effects model is a more conservative approach as its underlying assumption is closer to reality, particularly synthesising studies obtained only from the published literature, and it incorporates potential heterogeneity between studies when calculating the pooled estimates.[16 17] The heterogeneity between studies using the I2 statistic will be quantified. Where possible, subgroup analyses according to background characteristics, such as age, country and other potential characteristics will be implemented. Sensitivity analyses based on risk of bias in the studies will be carried out. Evidence of publication bias using funnel plots and statistically using Begg's and Egger's tests will be assessed.[18 19] The meta-analyses will be performed using Comprehensive Meta-Analysis, V.4.

Patient and public involvement

Development of this systematic review and meta-analysis protocol occurred without involvement of patients and the public.

ETHICS AND DISSEMINATION

Ethical approval is not required. The outcomes of this systematic review will be presented in conference presentations and published in peer-reviewed journals.

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