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Update and Summary of the European Association of Urology/ European Society of Paediatric Urology Paediatric Guidelines on Vesicoureteral Reflux in Children

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Abstract

Background and objective: The prescriptive literature on vesicoureteral reflux (VUR) is still limited and thus the level of evidence is generally low. The aim of these guidelines is to provide a practical approach to the treatment of VUR that is based on risk analysis and selective indications for both diagnostic tests and interventions. We provide a 2023 update on the chapter on VUR in children from the European Association of Urology (EAU) and European Society for Paediatric Urology (ESPU) guidelines.

Methods: A structured literature review was performed for all relevant publications published from the last update up to March 2022.

Key findings and limitations: The most important updates are as follows. Bladder and bowel dysfunction (BBD) is common in toilet-trained children presenting with urinary tract infection (UTI) with or without primary VUR and increases the risk of febrile UTI and focal uptake defects on a radionuclide scan. Continuous antibiotic prophylaxis (CAP) may not be required in every VUR patient. Although the literature does not provide any reliable information on CAP duration in VUR patients, a practical approach would be to consider CAP until there is no further BBD. Recommendations for children with febrile UTI and high-grade VUR include initial medical treatment, with surgical care reserved for CAP noncompliance, breakthrough febrile UTIs despite CAP, and symptomatic VUR that persists during long-term follow-up. Comparison of laparoscopic extravesical versus transvesicoscopic ureteral reimplantation demonstrated that both are good option in terms of resolution and complication rates. Extravesical surgery is the most common approach used for robotic reimplantation, with a wide range of variations and success rates.

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Conclusions and clinical implications: This summary of the updated 2023 EAU/ESPU guidelines provides practical considerations for the management and diagnostic evaluation of VUR in children.
Advancing practice: For children with VUR, it is important to treat BBD if present. A practical approach regarding the duration of CAP is to consider administration until BBD resolution.
Patient summary: We provide a summary and update of guidelines on the diagnosis and management of urinary reflux (where urine flows back up through the urinary tract) in children. Treatment of bladder and bowel dysfunction is critical, as this is common in toilet-trained children presenting with urinary tract infection.

1. Introduction

The aim of these guidelines is to provide a practical approach for the treatment of vesicoureteral reflux (VUR) that is based on risk analysis and selective indications for both diagnostic tests and interventions. The panel strongly shares the view that making simple and practical guidelines would underestimate the complexity of VUR as an endpoint for a wide range of underlying causes [1]. This publication is a summary of the 2023 update of the chapter on VUR in children from the European Association of Urology (EAU) and of the European Society for Paediatric Urology (ESPU) guidelines.

The lack of robust prospective randomised controlled trials limits the strength of established guidelines on the management of VUR. The scientific literature on VUR remains limited and thus the level of evidence is generally low. Most of the studies are retrospective, include heterogeneous patient groups, and have poor stratification of quality. Therefore, for children with VUR, it is unfortunately not possible to produce recommendations that are based on high-quality studies.

2. Methods

Chapters of the EAU/ESPU guidelines on paediatric urology are updated at regular intervals (every 4 yr). A previous summary of these guidelines was published in 2012 [2]. For this update of the chapter on VUR, a structured literature search was performed by a librarian and reviewed by at least two panel members for all relevant publications since the last update (June 2018) up to March 2022. Only English publications were eligible for inclusion. The literature search was performed using the following databases: MEDLINE, Embase, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews (via Ovid). We searched for Medical Subject Headings (MeSH) terms and free text words related to VUR AND reflux in paediatric patients, using Boolean operators. Variations of root words were searched. Conference abstracts were excluded (Supplementary material).

3. Results

3.1. Epidemiology, aetiology, and pathophysiology

Primary VUR is an anatomical and/or functional/physiological disorder with potentially serious consequences, such as focal uptake defects on a radionuclide scan, hypertension, and renal failure. Genetic analysis studies have revealed monogenic causes for VUR and significant differentiation of innate immunity and epithelial function genes in children with VUR/febrile urinary tract infections (UTIs) in comparison to control subjects [3–5].

Secondary VUR is caused by bladder outlet obstruction or neurogenic bladder dysfunction. In these patients, reflux often develops bilaterally and the grade of VUR can be directly correlated with the rise in bladder pressure due to bladder outlet obstruction, or neuropathological deterioration in a neurogenic bladder.

Primary VUR is a very common urological anomaly in children, with an incidence of nearly 1%. Among infants in whom hydronephrosis was prenatally identified on ultrasound (US) who were screened for VUR, the VUR prevalence was 16.2% (7–35%). Siblings of children with VUR had a 27.4% (3–51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2–61.4%) [6].

Febrile UTIs are more common for girls than for boys because of anatomical differences. However, among all children with febrile UTIs, boys are more likely to have VUR than girls (29% vs 14%). VUR by itself is not a cause of renal damage postnatally, but if associated with recurrent infections it can lead to renal scarring.

Evidence of a focal uptake defect on a radionuclide scan is present in 10–40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired postinfectious damage. Renal congenital damage is as a result of disordered renal development secondary to significant alterations in bladder disease. Acquired damage after pyelonephritis is thought to be due to a complex interaction of host and bacterial factors that lead to acute alterations in renal function and may lead to permanent renal scarring. This may have a negative impact on somatic growth and general wellbeing [7–9].

A focal uptake defect on a radionuclide scan is also a significant risk factor for breakthrough febrile UTI and may be used to determine those at risk of persistent symptomatic VUR [10].

Spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy (eg, duplex systems or an ectopic ureter). Faster resolution of VUR is more likely for age <1 yr at presentation, lower grade of reflux (grade I–III), and asymptomatic presentation with prenatal hydronephrosis or a sibling with VUR. Resolution is nearly 80% for VUR

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grades I and II and 30–50% for VUR grades III–V within 4–5 yr of follow-up. Spontaneous resolution is low for bilateral high-grade reflux [6]. In several Scandinavian studies, a complete resolution rate of >25% for high-grade VUR has been reported [11]. The presence of renal cortical abnormalities, bladder dysfunction, and breakthrough febrile UTIs are all negative predictive factors for VUR resolution [12,13].

Patients with higher grades of VUR often present with higher rates of focal uptake defects on radionuclide scans. Among those with prenatal hydronephrosis, a focal uptake defect on a radionuclide scan occurs in 10% of patients, whereas among patients with lower urinary tract dysfunction (LUTD) the prevalence may be as high as 30% [14]. Follow-up studies have shown that 10–20% of children with a focal uptake defect on a radionuclide scan develop hypertension or end-stage renal disease [15]. Furthermore, there is a clear co-prevalence of LUTD and VUR, which may be accompanied by bowel dysfunction [16].

3.2. Diagnostic evaluation

The diagnostic work-up should evaluate the overall health and development of the child (patient's height and weight, blood pressure), the presence of febrile UTI, renal status (serum creatinine and glomerular filtration rate [GFR]), the presence of VUR, and bladder and bowel function.

Standard imaging tests include renal and bladder US, voiding cystourethrography (VCUG) and nuclear renal scans. The standard modality for diagnosis of VUR is VCUG, especially for initial work-up. VUR is classified in five grades (Table 1) [17].

According to the literature, only a few studies have accurately investigated or compared radiation exposure in the diagnosis of VUR. Conflicting opinions on radiation dose exposure have arisen because of variability in VCUG protocols (total fluoroscopy time), differing radiological equipment, and radiation exposure from radionuclide studies in children with reduced renal function [18,19]. Alternative imaging modalities include contrast-enhanced voiding urosonography (ceVUS), magnetic resonance VCUG, and nuclear cystography [20,21]. However, despite concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard because it allows better determination of the grade of VUR (in a single or duplicate kidney) and assessment of the bladder and urethral configuration. A standardised protocol must be followed when performing VCUG [22].

Table 1 – Grading system for vesicoureteral reflux on voiding cystourethrography according to the International Reflux Study Committee

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter; marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

Intrarenal reflux is associated with a higher risk of developing renal scarring and it can be diagnosed on the images acquired during VCUG or on ceVUS [23,24]. Dimercaptosuccinic acid (DMSA) is considered to be the best nuclear agent for visualising cortical tissue and differential function between the two kidneys. Video-urodynamic studies are important in patients in whom secondary VUR is suspected, such as those with severe (neurogenic) bladder dysfunction or boys in whom VCUG is suggestive of posterior urethral valves (Table 2).

3.2.1. *Infants presenting with prenatally diagnosed hydronephrosis*

US of the kidneys and bladder is the standard initial postnatal evaluation tool. US should be delayed until the first week after birth because of early oliguria in neonates. The absence of hydronephrosis on postnatal US does not

Table 2 – Recommendations

Recommendation	Rating strength
For diagnosis of VUR apart from VCUG, ceVUS is another option.	Weak
Inform parents of children with VUR that siblings and offspring have a high prevalence of VUR.	Strong
Initially treat all symptomatic patients diagnosed within the first year of life with CAP, regardless of the grade of reflux or presence of focal uptake defects on a radionuclide scan.	Weak
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
Initially manage all children presenting at age 1–5 yr with medical treatment.	Strong
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
Ensure that a detailed investigation for the presence of LUTD is performed in all children and especially after toilet training. If LUTD is found, the initial treatment should always be for LUTD.	Strong
Offer reimplantation or endoscopic correction to patients with frequent breakthrough infections.	Weak
Offer reimplantation to patients with persistent high-grade reflux, and endoscopic correction for lower grades of reflux.	Strong
Offer surgical repair to children above the age of 1 yr presenting with high-grade reflux and abnormal renal parenchyma.	Weak
Offer surgical correction if parents prefer definitive therapy to conservative management.	Strong
Select the most appropriate management option based on: • The presence of a focal uptake defect on a radionuclide scan • Clinical course • The grade of reflux • Ipsilateral renal function • Bilaterality • Bladder function • Associated anomalies of the urinary tract • Age and sex • Compliance • Parental preference.Refer to Table 4 for risk factors and follow-up.	Weak
In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.	Strong

VUR = vescicoureteral reflux; VCUG = voiding cystourethrography; ceVUS = enhanced voiding urosonography; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction.

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exclude VUR. Bladder wall thickness and configuration may be an indirect sign of bladder outlet obstruction and VUR. The visualisation of cortical abnormalities with DMSA warrants the use of VCUG for detection of VUR in neonates/infants with prenatal hydronephrosis [6]. The panel recommends the use of VCUG in the setting of antenatally diagnosed hydronephrosis for patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, a solitary kidney with hydronephrosis, ureterocele, ureteric dilatation, abnormal bladders, and a history of febrile UTIs, as the likelihood of VUR is much higher. In infants with prenatal minimal renal pelvic dilatation and absent postnatal calicectasis, VCUG is not recommended, as VUR is rare in these cases and, if present, is like to be of low grade [25].

3.2.2. *Siblings and offspring of reflux patients*

The screening of asymptomatic siblings and offspring is controversial. Screening in all siblings and offspring cannot be recommended on the basis of the available evidence. It is recommended that families of children with VUR be informed that siblings and offspring have a higher chance of VUR and be educated about the signs and symptoms of UTIs (Table 2).

3.2.3. *Children with febrile UTIs*

Renal US should be performed as the initial evaluation for a febrile UTI and US should become part of follow-up to assess renal growth over time. US is the safest approach as the evidence for the criteria for selecting patients for reflux detection is weak. On diagnosing a child with a first febrile UTI, risk factors that include age (>6 mo), presence of sepsis, white blood cell count ($\geq$15 000/ml), and abnormal renal US results can be used to generate a predictive score for VUR presence [26]. The chapter on UTIs in the EAU/ESPU paediatric urology guidelines provides a diagnostic algorithm that can be followed for children with a febrile UTI.

Children with febrile infections and abnormal renal US findings have a higher risk of VUR and they should all be evaluated for VUR using VCUG [27]. If VUR is diagnosed, further evaluation has traditionally consisted of a DMSA scan, when available. A DMSA scan, when performed at the right time, can determine if there is renal scarring and the function of the individual kidneys and can be used to guide treatment options. The "top-down" approach is a strategy whereby an initial DMSA scan is carried out close to the time of a febrile UTI to determine the presence of acute pyelonephritis or a renal cortical abnormality, which is then followed by VCUG if the DMSA scan reveals kidney involvement [28–31]. This could especially be considered in children aged >1 yr given the invasiveness of the VCUG examination. Historically, the "bottom-up" approach was more common, whereby VCUG is first performed after an initial febrile UTI. A recent study used data from the Randomized Intervention for children with Vesicoureteral Reflux (RIVUR) and the Careful Urinary Tract Infection Evaluation (CUTIE) trials to compare the two approaches in terms of recurrent UTIs, VCUG, and use of continuous antibiotic prophylaxis (CAP). In this cohort of children the top-down approach was associated with higher incidence of subsequent recurrent febrile UTIs and a risk of missed VUR diagnoses, as well as significantly lower VCUG and CAP use in comparison to the bottom-up approach [32].

3.2.4. *Children with bladder and bowel dysfunction symptoms and VUR*

Detection of LUTD is essential when treating children with VUR. It is suggested that VUR with LUTD resolves faster after LUTD correction [33].

Among toilet-trained children, those with both LUTD and VUR are at higher risk of developing recurrent febrile UTIs than children with isolated VUR. Bladder and bowel dysfunction (BBD) is common in toilet-trained children presenting with UTI with or without primary VUR. It has also been shown that the presence of both BBD and VUR doubles the risk of UTI recurrence. Thus, all children presenting with UTIs should be carefully evaluated for the presence of BBD and managed accordingly, before any treatment of VUR. Effective management of BBD in these children may be as impactful as CAP [34].

In LUTD, VUR is often of low grade, US findings are normal, and there is no indication for performing VCUG. LUTD associated with febrile UTIs should be meticulously investigated with US and VCUG. Furthermore, any child for whom standard therapy for LUTD fails (reported in the chapter on "Day-time lower urinary tract conditions" in the EAU/ESPU guidelines) should undergo video-urodynamic investigation.

3.3. *Disease management*

The main management goal is preservation of kidney function by minimising the risk of pyelonephritis. Controversy persists over the optimal management of VUR, particularly in relation to the choice of diagnostic procedures and treatment, and the timing of treatment.

There are two main treatment approaches: conservative (medical) and surgical.

3.3.1. *Nonsurgical therapy*

The conservative approach includes watchful waiting, intermittent antibiotic prophylaxis or CAP, and bladder and bowel rehabilitation in those with LUTD [33,35,36].

Regular follow-up with imaging studies (US) and monitoring of the child's height and weight, as well as blood pressure and possibly serum creatinine, are part of the conservative management strategy to monitor spontaneous resolution of VUR and evaluate renal status. In the literature there is no consensus as to optimal timing or frequency of such studies. Follow-up should be tailored for each patient.

Assessment and management of all toilet-trained children presenting with febrile UTI should be part of conservative follow-up. During conservative management of high-grade infant VUR, spontaneous downgrading and resolution of VUR are more likely. However, this also depends on sex, breakthrough febrile UTI, the presence of a focal uptake defect on a radionuclide scan, and bladder dysfunction. There are practical scoring systems (Boston's Children Hospital VUR Resolution Rate Calculator or the iReflux Risk Calculator) for making decisions on further treatment, surveillance, prophylaxis, or surgical intervention.

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Circumcision during early infancy may be considered as part of the conservative approach because it is effective in reducing the risk of infection in normal children [37].

Conservative management should be dismissed in all cases of febrile breakthrough infections despite prophylaxis, and intervention should be considered.

3.3.1.1. CAP. Many prospective studies have evaluated the role of CAP in the prevention of recurrent febrile UTI and focal uptake defects on a radionuclide scan.

It is clear that CAP will not be required for every VUR patient. Trials have demonstrated that the benefit of CAP is none or minimal in low-grade reflux [38,39].

In a recent randomised controlled trial performed in 39 European centres (PREDICT), Morello et al. [40] assessed and quantified the efficacy of CAP in infants with grade III, IV, or V VUR and no previous UTIs. The number needed to treat for 2 yr to prevent one UTI was seven children, without any difference in kidney scarring, kidney function, or hospitalisation for UTIs. CAP provided just a small but significant benefit in preventing a first UTI despite an increase in the occurrence of non-*Escherichia coli* organisms and antibiotic resistance [40]. For children with VUR receiving CAP, younger age at initial diagnosis of febrile UTI ($\leq$12 mo), bilateral VUR, and BBD are all independent risk factors for the occurrence of breakthrough febrile UTIs [41]. Toilet-trained children and children with LUTD derive better benefit from CAP [42,43]. The RIVUR study showed that prophylaxis could reduce the risk of recurrent febrile UTI by 50%, but had no effect on a focal uptake defect on a radionuclide scan nor its consequences (hypertension and renal failure), and was associated with an increase in antimicrobial resistance [44,45]. Additional reviews of the RIVUR data using a risk classification system defined a high-risk group (uncircumcised males, presence of BBD, and high-grade reflux) that would benefit significantly from CAP. In the context of CAP in VUR patients, medical management should be viewed as a spectrum, with a shift from CAP in dilating VUR towards a selective, risk-based approach [46]. Decision-making may be influenced by the presence of risk factors for febrile UTI, such as young age, high-grade VUR, toilet-training status, LUTD, female sex, and circumcision status. Although the literature does not provide any reliable information about the duration of CAP in VUR patients, a practical approach would be to use CAP until BBD resolution.

Recommendation in the literature generally consist of prescribing daily antibiotics at a quarter to half of the regular therapeutic dose. Trimethoprim-sulfamethoxazole (TMP-SMZ), amoxicillin, and nitrofurantoin are the antibiotics most commonly used for CAP. TMP-SMZ must be avoided in infants aged <6 wk owing to the risk of hepatic injury and in children with severe renal insufficiency because of potential kidney toxicity. Nitrofurantoin is best avoided before the age of 4 mo owing to the risk of haemolytic anaemia [47,48]. In children with a breakthrough febrile UTI, a switch to an alternative antibiotic for prophylaxis may be considered. An antibiogram, if available, can help in choosing the most appropriate antibiotic. Children with a febrile UTI and high-grade VUR can still be considered for initial medical treatment, with surgical care reserved for CAP noncompliance, breakthrough febrile UTIs despite CAP, and symptomatic VUR (recurrent flank pain whether or not associated with febrile UTIs) that persists during long-term follow-up [41,49].

The optimal timing for CAP discontinuation is controversial; however, patients who have received CAP for <1 yr after the last febrile UTI and those with bilateral VUR are likely to have more frequent recurrences [50]. The surveillance protocol and the decision to perform either an antireflux procedure or to discontinue CAP should be individualised to each case and incorporate shared decision-making with the patient and caregivers. It is strongly advised that the risks, benefits, and alternatives be discussed in detail and that access to health care during febrile UTIs be taken into consideration.

One of the biggest concerns regarding CAP for patients, caregivers, and physicians is the long-term effects. As a secondary outcome of the RIVUR study, TMP-SMZ prophylaxis for 2 yr was not associated with any adverse effect on complete blood count, serum electrolytes, or creatinine. Routine laboratory tests in otherwise healthy children are not mandatory [51]. The impact of long-term CAP on the gut microbiota in children with VUR is controversial and requires further research [52,53].

CAP can prevent new febrile UTIs in children with a history of febrile UTIs in the context of antenatal hydronephrosis with presumed or confirmed VUR. However, the literature remains ambiguous as to whether infants diagnosed with asymptomatic VUR during the antenatal hydronephrosis work-up might also benefit from CAP (Table 2) [54].

3.3.2. Surgical therapy

Surgical treatment can be carried out via endoscopic injection of bulking agents or ureteral reimplantation (open vs minimally invasive). In children with recurrent febrile UTIs and hypofunctioning renal units, nephrectomy may be an option.

3.3.2.1. Subureteric injection of bulking material. With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of VUR in children. Reflux timing during VCUG can be used to predict the success of endoscopic treatment, since the success rate is higher for VUR occurring only during the voiding phase than for the filling-phase VUR [55].

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon). Owing to concerns about particle migration, PTFE is not approved for use in children. Currently, a solution of dextranomer/hyaluronic acid (D/HA; Deflux, Dexell) and a polyacrylate-polyalcohol copolymer (PPC) hydrogel (Vantris) are most commonly used [56].

In a meta-analysis of 5527 patients and 8101 renal units, the reflux resolution rate (by ureter) following one treatment was 78.5% for grade I and II reflux, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate

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of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicate (50%) versus single (73%) systems, and for neuropathic (62%) versus normal (74%) bladders. The injection volume required to achieve the same success rate can differ between agents and is generally less for PPC than for D/HA [57–59].

Acquired vesicoureteral junction obstruction (VUJO) can also occur as a long-term complication after endoscopic correction of VUR. Obstruction seems to be more common for BBD patients. Patients with high-grade reflux and dilated ureters are at risk of late obstruction. Although success rates following short-term follow-up (3–6 mo) and VUJO rates appear to be comparable between various bulking agents, longer-term follow-up studies have claimed that there is a higher VUJO rate when PPC is used as the bulking material. However, early and delayed obstruction after Deflux injection was reported for <1% of patients. Most cases resolved after temporary double-J stenting, but some required open reimplantation, independent of the substance injected [60–64]. Although it has been shown that ureteric fibrosis and/or inflammatory changes following PPC injection are similar to those after injection of other materials, PPC has continued to demonstrate higher obstruction rates [65].

The added benefit of endoscopic correction of VUR over CAP alone remains uncertain owing to the few studies with low methodological quality. Although there was a significant reduction in the incidence of febrile UTI, there were

Table 3 – Summary of evidence and recommendations for the management of vesicoureteric reflux in childhood

Summary of evidence
There is no evidence that correction of persistent low-grade reflux (grades I–III) without symptoms and normal kidneys offers a significant benefit.
The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in cases of breakthrough infection and a new focal uptake defect on a radionuclide scan needs to be challenged, because the treatment should be tailored to different risk groups.
Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of reimplantation is better than for endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved with endoscopic injection for lower grades.
The choice of management depends on the presence of a focal uptake defect on a radionuclide scan, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference. Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for a new focal uptake defect on a radionuclide scan.

LUTD = lower urinary tract dysfunction; UTI = urinary tract infection.

Table 4 – Management and follow-up according to risk category

Risk category	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet training with high-grade reflux (grade IV–V), abnormal kidneys, and LUTD	Initial treatment is always for LUTD with CAP; an intervention may be considered in cases of BT infections or persistent VUR	Greater possibility of earlier intervention	More aggressive follow-up for febrile UTI and LUTD; full re-evaluation after 6 mo
High	Symptomatic male or female patients after toilet training with high-grade reflux (grade IV–V), abnormal kidneys, and no LUTD	An intervention should be considered	Reimplantation has better results than endoscopic surgery	Postoperative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet training with high-grade reflux and abnormal kidneys	CAP is the initial treatment; an intervention may be considered in cases of BT infections or persistent VUR	Spontaneous resolution is higher in males	Follow-up for febrile UTI/hydronephrosis; full re-evaluation after 12–24 mo
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment; an intervention may be considered in cases of BT infections or persistent VUR		Follow-up for febrile UTI/hydronephrosis; full re-evaluation after 12–24 mo
Moderate	Symptomatic male or female patients after toilet training with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP; an intervention may be considered in cases of BT infections or persistent VUR	In cases with persistent LUTD despite urotherapy, an intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet training with low-grade reflux and abnormal kidneys with or without LUTD	The choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for febrile UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, low-grade reflux, and LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, low-grade reflux, and no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about the risk of infection	Follow-up for febrile UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about the risk of infection	Follow-up for febrile UTI

LUTD = lower urinary tract dysfunction; CAP = continuous antibiotic prophylaxis; UTI = urinary tract infection; VCUG = voiding cystourethrography; PNH = prenatal diagnosed hydronephrosis; BT = breakthrough.

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no differences in either symptomatic UTI or renal damage [39].

The ureteral diameter ratio is a relatively recent objective measurement and appears to be a new tool for predicting clinical outcomes and success after endoscopic injection for VUR [66]. Clinical validation of the effectiveness of antireflux endoscopy is currently hampered by the lack of methodologically appropriate studies.

3.3.2.2. Open surgical techniques. Various intravesical and extravesical techniques have been described for surgical correction of VUR. Although different methods have specific advantages and complications, most share the basic principle of lengthening the intramural part of the ureter via submucosal embedding of the ureter. All techniques have been shown to be safe, with a low rate of complications and excellent success rates (92–98%) [67]. Overall, all surgical procedures offer very high and similar success rates for VUR correction.

3.3.2.3. Laparoscopic and robot-assisted laparoscopic techniques. A considerable number of case series of patients undergoing transperitoneal, extravesical, and pneumovesicoscopic intravesical ureteral reimplantation have demonstrated the feasibility of these techniques. A recent systematic review and meta-analysis comparing laparoscopic extravesical ureteral reimplantation (LEVUR) versus transvesicoscopic ureteral reimplantation (TVUR) revealed that both are good options in terms of resolution and complication rates. LEVUR is generally preferred for unilateral low-grade cases and currently appears to have a higher success rate and a shorter hospital stay [61,68].

A number of antireflux surgeries have been performed robotically, with an extravesical approach most commonly used. Two recent systematic reviews analysed outcomes for open ureteral reimplantation (OUR) and robot-assisted laparoscopic ureteral reimplantation (RALUR). In the first comparing OUR to RALUR, the robotic approach was considered a feasible, and effective surgical approach for primary paediatric VUR, with similar success rates [69,70]. In the second systematic review, operative times, costs, and rates of postoperative complications requiring secondary intervention were higher with RALUR, but postoperative pain and hospital length of stay were lower in comparison to OUR [71].

In addition, laparoscopic and robot-assisted approaches are more invasive than endoscopic correction and potential advantages over open surgery continue to be analysed. Therefore, a laparoscopic approach cannot be recommended as a routine procedure at present. In centres with established experience, laparoscopic surgery can be offered to parents/caregivers as an alternative treatment option [72,73]. Older children with complex anatomy and/or following a failed injection or open reimplantation could benefit from RALUR, as a robotic approach can facilitate better exposure. RALUR can be performed unilaterally or bilaterally, although caution is advised in bilateral cases owing to the risk of transient urinary retention. De novo hydronephrosis can occur in up to 30% of cases after extravesical RALUR and is similar to that observed after open ureteral reimplantation, which is self-resolving in the overwhelming majority of cases (Tables 3 and 4) [74].

4. Conclusions

The most important updates are as follows.

- **Epidemiology, aetiology, and pathophysiology**: Genetic analyses have revealed monogenic causes for VUR and significant differentiation of innate immunity and epithelial function genes in children with VUR/febrile UTIs in comparison to control subjects.
- **Diagnostic evaluation**: The diagnostic work-up should evaluate the overall health and development of the child (height and weight, blood pressure), febrile UTI, renal status (serum creatinine and GFR), VUR, and bladder and bowel function. US of the kidney and bladder is the first postnatal standard evaluation tool. VCUG is recommended in patients with US findings of:
  - o Bilateral high-grade hydronephrosis
  - o Duplex kidneys with hydronephrosis of the lower pole and breakthrough febrile UTIs
  - o A solitary kidney with hydronephrosis
  - o A ureteric dilatation
  - o Abnormal bladders and a history of febrile UTIs (because the likelihood of VUR is much higher).

  DMSA is the best agent for visualising cortical tissue and differential kidney function. Screening of asymptomatic siblings and offspring is controversial. Children with febrile infections and abnormal renal US findings have a higher risk of VUR and should be evaluated using VCUG. Among toilet-trained children, those with both LUTD and VUR are at higher risk of recurrent febrile UTIs than children with isolated VUR. BBD is common among toilet-trained children presenting with a febrile UTI with or without primary VUR. The presence of both BBD and VUR doubles the risk of recurrent febrile UTI, so all children presenting with UTI should be carefully evaluated for BBD and managed accordingly, before treatment of VUR.
- **Disease management**: The main management goal is preservation of renal function. There are two main treatment approaches. The nonsurgical approach includes watchful waiting, intermittent antibiotic prophtlaxis or CAP, and BBD rehabilitation in those with LUTD. Regular follow-up involves imaging and monitoring of height and weight as well as blood pressure and possibly serum creatinine to monitor spontaneous resolution of VUR and evaluate kidney status. The surgical approach can involve endoscopic injection of bulking agents or ureteral reimplantation (open vs minimally invasive).
- **CAP**: CAP may not be needed in every VUR patient and generally consists of daily antibiotics given at a quarter to half of the regular therapeutic dose. In the PREDICT trial, CAP provided a small but significant benefit for infants with grade III–V VUR and no previous UTIs in preventing a first UTI, at the cost of an increase in non-*E. coli* organisms and antibiotic resistance. A practical approach is to use CAP until BBD resolution. Initial medical management can be considered for a child with a febrile UTI and high-grade VUR, with surgical options reserved

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for CAP noncompliance, breakthrough febrile UTIs despite CAP, and persistent symptomatic VUR during long-term follow-up.

- **Endoscopic treatment**: VUJO may develop during long term follow-up after endoscopic correction of VUR. Patients with high-grade reflux and dilated ureters are at higher risk of late VUJO despite comparable success and VUJO rates over short-term (3–6 mo) follow-up. For high-grade VUR in infants, injection therapy has a higher resolution rate than CAP. However, endoscopic treatment cannot be recommended for all high-grade reflux cases, as not all are symptomatic. VUR resolution or downgrading must be taken into account and is more likely to be observed under favourable conditions such as unilateral reflux, lower reflux grades, and high voiding efficiency. The ureteral diameter ratio is a new tool for predicting clinical outcomes and success after endoscopic injection for VUR.
- **Surgical treatment**: A recent systemic review and meta-analysis revealed that LEVUR and TVUR are good alternatives in terms of resolution and complication rates. Several antireflux surgical procedures have been performed robotically, most commonly via an extravesical approach. RALUR can be considered as a feasible and effective surgical approach for primary paediatric VUR, with equivalent success rates to OUR.

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References

[1] Lee T, Ellimoottil C, Marchetti KA, et al. Impact of clinical guidelines on voiding cystourethrogram use and vesicoureteral reflux incidence. J Urol 2018;199:831–6.
[2] Tekgül S, Riedmiller H, Hoebeke P, et al. EAU guidelines on vesicoureteral reflux in children. Eur Urol 2012;62:534–42.
[3] Shahrokhzadeh S, Soleimani A, Kordi-Tamandani DM, Sangtarash MH, Nejati O, Taheri M. Association of genetic polymorphisms in GSTP1, GSTM1, and GSTT1 genes with vesicoureteral reflux susceptibility in the children of Southeast Iran. Iran J Public Health 2020;49:1364–71.
[4] Liu JL, Shen Q, Wu MY, et al. Responsible genes in children with primary vesicoureteral reflux: findings from the Chinese Children Genetic Kidney Disease Database. World J Pediatr 2021;17:409–18.
[5] Liang D, McHugh KM, Brophy PD, et al. DNA copy number variations in children with vesicoureteral reflux and urinary tract infections. PLoS One 2019;14:e0220617.
[6] Skoog SJ, Peters CA, Arant Jr BS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. J Urol 2010;184:1145–51.
[7] Mohanan N, Colhoun E, Puri P. Renal parenchymal damage in intermediate and high grade infantile vesicoureteral reflux. J Urol 2008;180:1635–8.
[8] Olbing H, Smellie JM, Jodal U, Lax H. New renal scars in children with severe VUR: a 10-year study of randomized treatment. Pediatr Nephrol 2003;18:1128–31.
[9] Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. J Urol 2010;184:265–73.
[10] Loukogeorgakis SP, Burnand K, MacDonald A, et al. Renal scarring is the most significant predictor of breakthrough febrile urinary tract infection in patients with simplex and duplex primary vesicoureteral reflux. J Pediatr Urol 2020;16:189e1–7.
[11] Esbjörner E, Hansson S, Jakobsson B. Management of children with dilating vesico-ureteric reflux in Sweden. Acta Paediatr 2004;93:37–42.
[12] Schwab Jr CW, Wu HY, Selman H, Smith GH, Snyder 3rd HM, Canning DA. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. J Urol 2002;168:2594–9.
[13] Sillén U, Brandström P, Jodal U, et al. The Swedish reflux trial in children: V. Bladder dysfunction. J Urol 2010;184:298–304.
[14] Ylinen E, Ala-Houhala M, Wikström S. Risk of renal scarring in vesicoureteral reflux detected either antenatally or during the neonatal period. Urology 2003;61:1238–42.
[15] Mathias S, Greenbaum LA, Shubha AM, Raj JAM, Das K, Pais P. Risk factors for renal scarring and clinical morbidity in children with high-grade and low-grade primary vesicoureteral reflux. J Pediatr Urol 2022;18:225.e1–e8.
[16] Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol 1998;160:1019–22.
[17] Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol 1985;15:105–9.
[18] Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011;128:595–610.
[19] Page M, Florescu C, Johnstone L, Habteslassie D, Ditchfield M. Paediatric urological investigations–dose comparison between urology-related and CT irradiation. Pediatr Radiol 2013;43:846–50.
[20] Murakami N, Kawada JI, Watanabe A, et al. Ureteral dilatation detected in magnetic resonance imaging predicts vesicoureteral reflux in children with urinary tract infection. PLoS One 2018;13:e0209595.
[21] Oh S, Ha JY, Cho YJ. Contrast-enhanced voiding ultrasonography to detect intrarenal reflux in children: comparison with ^{99m}Tc-DMSA renal scans. Ultrasonography 2022;41:502–10.
[22] Janssen KM, Kirsch AJ, Crisostomo-Wynne TC, Leong T, Cuda SP, Arlen AM. Standardized protocol for voiding cystourethrogram: are recommendations being followed? J Pediatr Urol 2021;17:66.e1–.

[23] Simicic Majce A, Arapovic A, Saraga-Babic M, et al. Intrarenal reflux in the light of contrast-enhanced voiding urosonography. Front Pediatr 2021;9:642077.
[24] Schneider KO, Lindemeyer K, Kammer B. Intrarenal reflux, an overlooked entity — retrospective analysis of 1,166 voiding cysturethrographies in children. Pediatr Radiol 2019;49:617–25.
[25] Coplen DE, Austin PF, Yan Y, Dicke JM. Correlation of prenatal and postnatal ultrasound findings with the incidence of vesicoureteral reflux in children with fetal renal pelvic dilatation. J Urol 2008;180:1631–4.
[26] Lertdumrongluk K, Lertdumrongluk P. Predictive score for vesicoureteral reflux in children with a first febrile urinary tract infection. Int J Urol 2021;28:573–7.
[27] Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. JAMA Pediatr 2014;168:893–900.
[28] Quirino IG, Silva JM, Diniz JS, et al. Combined use of late phase dimercapto-succinic acid renal scintigraphy and ultrasound as first line screening after urinary tract infection in children. J Urol 2011;185:258–63.
[29] Hansson S, Dhamey M, Sigstrom O, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol 2004;172:1071–3.
[30] Herz D, Merguerian P, McQuiston L, Danielson C, Gheen M, Brenfleck L. 5-Year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. J Urol 2010;184:1703–9.
[31] Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. J Pediatr 2007;151:581–584.e1.
[32] Scott Wang HH, Cahill D, Panagides J, Logvinenko T, Nelson C. Top-down versus bottom-up approach in children presenting with urinary tract infection: comparative effectiveness analysis using RIVUR and CUTIE data. J Urol 2021;206:1284–90.
[33] Colen J, Docimo SG, Stanitski K, et al. Dysfunctional elimination syndrome is a negative predictor for vesicoureteral reflux. J Pediatr Urol 2006;2:312–5.
[34] Meena J, Mathew G, Hari P, Sinha A, Bagga A. Prevalence of bladder and bowel dysfunction in toilet-trained children with urinary tract infection and/or primary vesicoureteral reflux: a systematic review and meta-analysis. Front Pediatr 2020;8:84.
[35] Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev 2019;2019:CD001534.
[36] Dias CS, Silva JM, Diniz JS, et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J 2010;29:139–44.
[37] Chan JY, Khondker A, Lee MJ, et al. The role of circumcision in preventing urinary tract infections in children with antenatal hydronephrosis: systematic review and meta-analysis. J Pediatr Urol 2023;19:766–77.
[38] de Bessa Jr J, de Carvalho Mrad FC, Mendes EF, et al. Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. J Urol 2015;193:1772–7.
[39] Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev 2019;2019:CD001532.
[40] Morello W, Baskin E, Jankauskiene A, et al. Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. N Engl J Med 2023;389:987–97.
[41] Su D, Shen Q, Zhai Y, et al. Risk factors for breakthrough urinary tract infection in children with vesicoureteral reflux receiving continuous antibiotic prophylaxis. Transl Pediatr 2022;11:1–9.
[42] Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006;117:626–32.
[43] Montini G, Rigon L, Zucchetta P, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics 2008;122:1064–71.
[44] Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014;370:2367–76.
[45] Mathews R, Mattoo TK. The role of antimicrobial prophylaxis in the management of children with vesicoureteral reflux—the RIVUR study outcomes. Adv Chronic Kidney Dis 2015;22:325–30.
[46] Wang ZT, Wehbi E, Alam Y, Khoury A. A reanalysis of the RIVUR trial using a risk classification system. J Urol 2018;199:1608–14.
[47] Kemnic TR, Coleman M. Trimethoprim sulfamethoxazole. StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
[48] Nickavar A, Sotoudeh K. Treatment and prophylaxis in pediatric urinary tract infection. Int J Prev Med 2011;2:4–9.
[49] Xie M, Xu X, Cao Z, Xiao H. Do various treatment modalities of vesicoureteral reflux have any adverse effects in pediatric patients? A meta-analysis. Urol Int 2021;105:1002–10.
[50] Anraku T, Obara K, Tasaki M, Tomita Y. Retrospective analysis to determine the optimal timing to discontinue continuous antibiotic prophylaxis in patients with primary vesicoureteral reflux. Urol Int 2019;102:462–7.
[51] Nadkarni MD, Mattoo TK, Gravens-Mueller L, et al. Laboratory findings after urinary tract infection and antimicrobial prophylaxis in children with vesicoureteral reflux. Clin Pediatr 2020;59:259–65.
[52] Morello W, D'Amico F, Serafinelli J, et al. Low-dose antibiotic prophylaxis induces rapid modifications of the gut microbiota in infants with vesicoureteral reflux. Front Pediatr 2021;9:674716.
[53] Akagawa Y, Kimata T, Akagawa S, et al. Impact of long-term low dose antibiotic prophylaxis on gut microbiota in children. J Urol 2020;204:1320.
[54] Leigh J, Rickard M, Sanger S, Petropoulos J, Braga LH, Chanchlani R. Antibiotic prophylaxis for prevention of urinary tract infections in the first year of life in children with vesicoureteral reflux diagnosed in the workup of antenatal hydronephrosis: a systematic review. Pediatr Nephrol 2020;35:1639–46.
[55] Han DS, Cambareri G, Alagiri M, Chiang G. Reflux timing is a predictor of successful endoscopic treatment of vesicoureteral reflux. Urology 2019;124:237–40.
[56] Cohen S, Kocherov S, Jaber J, et al. Multicenter survey of endoscopic treatment of vesicoureteral reflux utilizing polyacrylate-polyalcohol-bulking copolymer (Vantris) in patients with duplex systems. J Pediatr Endosc Surg 2021;3:205–9.
[57] Elder JS, Diaz M, Caldamone AA, et al. Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. J Urol 2006;175:716–22.
[58] Garcia-Aparicio L, Blazquez-Gomez E, Martin O, et al. Randomized clinical trial between polyacrylate-polyalcohol copolymer (PPC) and dextranomer-hyaluronic acid copolymer (Dx/HA) as bulking agents for endoscopic treatment of primary vesicoureteral reflux (VUR). World J Urol 2018;36:1651–6.
[59] Tekin A, Yagmur I, Tiryaki S, Dokumcu Z, Ulman I, Avanoglu A. Changing bulking agent may require change in injection volume for endoscopic treatment of vesicoureteral reflux. Int Braz J Urol 2018;44:1194–9.
[60] Escolino M, Kalfa N, Castagnetti M, et al. Endoscopic injection of bulking agents in pediatric vesicoureteral reflux: a narrative review of the literature. Pediatr Surg Int 2023;39:133.
[61] Babu R, Chandrasekharam VVS. A systematic review & meta-analysis comparing outcomes of endoscopic treatment of primary vesico ureteric reflux in children with polyacrylate poly alcohol copolymer versus dextranomer hyaluranic acid. J Pediatr Surg 2022;57:683–9.
[62] Ben-Meir D, Bahouth Z, Halachmi S. Late-onset uretero-vesical junction obstruction following endoscopic injection of bulking material for the treatment of vesico-ureteral reflux. Urology 2017;101:60–2.
[63] Dothan D, Kocherov S, Jaber J, Chertin B. Endoscopic correction of reflux utilizing polyacrylate polyalcohol bulking copolymer (Vantris) as a tissue augmenting substance: lessons learned over the 10 years of experience. J Laparoendosc Adv Surg Tech 2021;31:1073–8.
[64] Okawada M, Murakami H, Tanaka N, et al. Incidence of ureterovesical obstruction and Cohen antireflux surgery after Deflux® treatment for vesicoureteric reflux. J Pediatr Surg 2018;53:310–2.
[65] Chertin B, Mele E, Kocherov S, Zilber S, Gerocarni Nappo S, Capozza N. What are the predictive factors leading to ureteral obstruction

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following endoscopic correction of VUR in the pediatric population? J Pediatr Urol 2018;14:538.

[66] Payza AD, Hosgor M, Serdaroglu E, Sencan A. Can distal ureteral diameter measurement predict primary vesicoureteral reflux clinical outcome and success of endoscopic injection? J Pediatr Urol 2019;15:515.

[67] Duckett JW, Walker RD, Weiss R. Surgical results: International Reflux Study in Children—United States branch. J Urol 1992;148:1674–5.

[68] Babu R, Chandrasekharam VVS. A systematic review and meta-analysis comparing outcomes of laparoscopic extravesical versus trans vesicoscopic ureteric reimplantation. J Pediatr Urol 2020;16:783–9.

[69] Deng T, Liu B, Luo L, et al. Robot-assisted laparoscopic versus open ureteral reimplantation for pediatric vesicoureteral reflux: a systematic review and meta-analysis. World J Urol 2018;36:819–28.

[70] Feng S, Yu Z, Yang Y, Bi Y, Luo J. Minimally invasive versus open ureteral reimplantation in children: a systematic review and meta-analysis. Eur J Pediatr Surg. In press. https://doi.org/10.1055/s-0043-1764321.

[71] Esposito C, Castagnetti M, Autorino G, et al. Robot-assisted laparoscopic extra-vesical ureteral reimplantation (Ralur/Revur) for pediatric vesicoureteral reflux: a systematic review of literature. Urology 2021;156:e1–e11.

[72] Bowen DK, Faasse MA, Liu DB, Gong EM, Lindgren BW, Johnson EK. Use of pediatric open, laparoscopic and robot-assisted laparoscopic ureteral reimplantation in the United States: 2000 to 2012. J Urol 2016;196:207–12.

[73] Grimsby GM, Dwyer ME, Jacobs MA, et al. Multi-institutional review of outcomes of robot-assisted laparoscopic extravesical ureteral reimplantation. J Urol 2015;193:1791–5.

[74] Kim C. Robotic urologic surgery in infants: results and complications. Front Pediatr 2019;7:187.

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