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Collaborative Review – Pediatric Urology

Vesicoureteral Reflux: Current Trends in Diagnosis, Screening, and Treatment

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Abstract

Context: Vesicoureteral reflux (VUR) is present in approximately 1% of children in North America and Europe and is associated with an increased risk of pyelonephritis and renal scarring. Despite its prevalence and potential morbidity, however, many aspects of VUR management are controversial.
Objective: Review the evidence surrounding current controversies in VUR diagnosis, screening, and treatment.
Evidence acquisition: A systematic review was performed of Medline, Embase, Prospero, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, clinicaltrials.gov, and the most recent guidelines of relevant medical specialty organizations.
Evidence synthesis: We objectively assessed and summarized the published data, focusing on recent areas of controversy relating to VUR screening, diagnosis, and treatment.
Conclusions: The evidence base for many current management patterns in VUR is limited. Areas that could significantly benefit from additional future research include improved identification of children who are at risk for VUR-related renal morbidity, improved stratification tools for determining which children would benefit most from which VUR treatment option, and improved reporting of long-term outcomes of VUR treatments.

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1. Introduction

From a historical perspective, urinary tract infection (UTI) in general and acute pyelonephritis (APN) in particular have long been linked with patient morbidity [1]. By the mid- to late 20th century, vesicoureteral reflux (VUR) had come to be understood as a link between UTI, APN, renal scarring, and end-stage renal disease [2,3]. With advances in the safety and efficacy of antimicrobials [4] and an improved understanding of the likelihood of spontaneous resolution [5], by the 1970s, continuous antibiotic prophylaxis (CAP) had become standard initial management of patients with VUR [6]. For those with recurrent or breakthrough UTI or unresolved VUR, surgical management by ureteroneocystostomy was the treatment of choice [7,8]. In the 1980s, surgical management for select patients became less invasive with the development of endoscopic injection (EI) as an alternative treatment [9,10].

However, an evolving body of literature raised doubts regarding these treatment options. The first two major

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randomized controlled trials (RCT) of VUR, the International Reflux Study and the Birmingham Reflux Study, revealed a relatively low rate of de novo renal sequelae in VUR patients despite frequent preexisting scarring (typically defined by intravenous urography) [11,12]. Perhaps more important, both these and subsequent studies found medical and surgical management of VUR equivalent at preventing long-term renal damage [13,14]. More recently, multiple trials have demonstrated similar UTI rates among patients who were and were not on CAP, most of whom had low- to moderate-severity VUR [15–19]. Other studies have concluded that CAP is indeed effective in preventing UTI, particularly in patients with high-grade reflux [20,21]. Still other research has shown that although VUR is clearly associated with renal scarring, VUR is neither necessary nor sufficient for the development of APN and renal scarring [22].

Against this backdrop of uncertainty, multiple medical organizations have weighed in on the evaluation and management of pediatric UTI and VUR through the publication of clinical practice guidelines [23–29]. Conflicting data (and conflicting opinions) make it difficult to determine which children with VUR will benefit from surgical correction, from EI, or from CAP. It is similarly unclear which patients require no treatment of any kind. The objective of this collaborative review is therefore to analyze the best available evidence underlying current practices in VUR screening, diagnosis, and treatment.

2. Evidence acquisition

In May 2011, we searched Medline, Embase, the Cochrane Database of Systematic Reviews, and Prospero for English-language studies using the exploded search term *vesicoureteral reflux;* additional selective searches were performed using *urinary tract infection, renal scar,* and *pyelonephritis,* each limited by *pediatric, child,* or *children.* We focused on articles published since the year 2000; occasional older papers were included if they were of particular historical or clinical significance.

We identified ongoing or recently completed trials using the Cochrane Central Register of Controlled Trials and clinicaltrials.gov. Reference lists of included publications were hand-searched for any significant studies. We also reviewed and synthesized the published guidelines of relevant scientific and medical groups: the European Association of Urology (EAU)/European Society for Pediatric Urology (ESPU) [29], the American Urological Association (AUA) [25,27], the American Academy of Pediatrics (AAP) [28], the European Society of Pediatric Radiology (ESPR) [26], the American College of Radiology/Society of Pediatric Radiology [23], the Society for Fetal Urology (SFU) [30], and the National Institute for Health and Clinical Excellence (NICE) [24].

3. Evidence synthesis

3.1. *Diagnosis of vesicoureteral reflux in children after a febrile urinary tract infection*

In 1999, the AAP recommended that a renal/bladder ultrasound (RBUS) and voiding cystourethrogram (VCUG) be obtained after a first febrile UTI in children 2–24 mo of age [31]. This recommendation was based on contemporary understanding of reflux nephropathy, that is, that VUR in the setting of UTI leads to APN, in turn leading to renal scarring and long-term sequelae. VUR could therefore preemptively be identified and treated with CAP or surgery, thus decreasing renal outcomes such as hypertension [32–34] and renal failure [35,36].

However, there has been a gradual drift away from the 1999 AAP guidelines. In two studies of compliance with these guidelines, one reported that only 39.5% of children received a VCUG following their first UTI, while only 44% underwent RBUS [37]. In another, only 61% of children received a VCUG, with racial or ethnic minorities and uninsured patients being disproportionately less likely to undergo imaging [38]. Many authors have cited concerns over radiation exposure or the discomfort of urethral catheterization as barriers to obtaining recommended

Table 1 – Clinical guidelines for evaluating children with febrile urinary trace infection

Organization	Initial imaging tests	Indications for VCUG	Indications for DMSA
EAU/ESPU [29]	RBUS and (VCUG or DMSA)	Initial febrile UTI, initial UTI (boys), or recurrent UTI (girls)	Initial febrile UTI
AAP [28]	RBUS	Recurrent UTI, hydroureter, hydronephrosis, renal scar	Not recommended outside of research studies
ESPR [26]	RBUS and DMSA	Evidence of renal involvement of DMSA	Initial febrile UTI
NICE [24]	RBUS	Age <6 mo: recurrent or atypical UTI Age 6 mo to 3 yr: recurrent or atypical UTI AND hydroureter, hydronephrosis, family history of VUR, non–*E. coli* infection, or poor urine flow Age >3 yr: None	Age <3 yr: recurrent or atypical UTI Age >3 yr: recurrent UTI only

VCUG = voiding cystourethrogram; DMSA = technetium 99m Tc dimercaptosuccinic acid; EAU = European Association of Urology; ESPU = European Society for Pediatric Urology; RBUS = renal/bladder ultrasound; UTI = urinary tract infection; AAP = American Academy of Pediatrics; ESPR = European Society of Pediatric Radiology; NICE = National Institute for Health and Clinical Excellence; VUR = vesicoureteral reflux; *E. coli* = *Escherichia coli.*

imaging [39]. One prospective study of children after their first febrile UTI found RBUS to be normal in 88%, whereas only 39% were found to have VUR, 96% of whom had low-grade reflux [40].

Therefore, the AAP recently revised its guidelines (Table 1): Only RBUS is now recommended after an initial febrile UTI [28]. VCUG is recommended only for recurrent UTI or when RBUS reveals ureteral dilation or renal abnormalities. The AAP also counsels families to seek medical attention within 48 h if fever persists or recurs [28], although whether delayed diagnosis increases the likelihood of renal scar formation in children is controversial [41–44].

In contrast, the EAU/ESPU guidelines recommend initial evaluation with VCUG in addition to RBUS [29]. The AUA guidelines, meanwhile, only address the management of children following diagnosis [25]. Both the EAU/ESPU and AUA guidelines note that technetium 99m Tc dimercaptosuccinic acid (DMSA) scans can be an option following diagnosis, particularly in patients with breakthrough UTI, high-grade VUR, or elevated creatinine.

In contrast, the ESPR has endorsed a fundamentally different philosophy of post-UTI imaging recommendations, one that focuses more on kidney involvement (colloquially known as the *top-down approach*) [26]. The goal of this approach is to determine the presence or absence of APN, renal dysplasia, or acquired renal scarring. Evaluation thus begins with RBUS and DMSA renal scan; VCUG is performed only if renal involvement is identified. Benefits to this approach include decreased urethral catheterizations, decreased ionizing radiation to the gonads, and decreased detection of "clinically insignificant" VUR not involving the kidneys [39,45]. Retrospective and prospective studies have demonstrated that use of the top-down approach could reduce the number of VCUGs performed while missing a VUR diagnosis in a minority of children with high-grade reflux [45–48].

A critical assumption behind the top-down approach is that VUR in the absence of scintigraphic abnormality does not lead to future renal damage. If this assumption is valid, then the potential cost savings to health systems are huge, both in terms of financial (decreased use of costly testing and interventions) and human (decreased anxiety over said testing and interventions) factors. Nevertheless, potential limitations to the top-down approach must be taken into consideration. A recent meta-analysis has shown DMSA to perform poorly at detecting high-grade VUR, with sensitivity and specificity of only 79% and 53%, respectively [49]. Although many would consider this conclusion cause for concern, advocates for the top-down approach would rightfully point out that the presence or absence of VUR—even high-grade VUR—is irrelevant to their central philosophy, which is focused on the presence or absence of kidney damage. By this reasoning, only in the presence of renal parenchymal involvement does VUR truly matter.

There is also a significant degree of interinstitutional variability in how DMSA scans are performed. In one recent survey of children's hospitals, the administered isotope dose varied among institutions an average of 3-fold—and in some cases up to 20-fold—per child [50]. Investigators with the Randomized Intervention in Vesico-Ureteral Reflux (RIVUR) study describe similar variability in DMSA dose and quality, despite long-standing dosing guidelines [51]; 17% of RIVUR DMSA scans were rejected because of poor quality [52]. With growing concerns regarding the effect of radiation on long-term carcinogenesis risk [53,54], this increased dosage should be taken into account when deciding the best course of evaluation for a given patient.

On average in the United States, DMSA is more expensive than VCUG and delivers a higher effective radiation dose than VCUG, albeit to the kidney rather than the pelvis. For a single imaging encounter, top-down would cost US $329 and deliver 0.52 mSv more per patient than would VCUG and RBUS [48]. However, these estimates account for neither the costs of repeated testing nor of VUR treatment, both of which are significant. Proponents of the top-down approach would argue that identifying all patients with VUR by VCUG leads to both treatment and follow-up imaging of all patients with VUR, including children with low-grade VUR who are at low risk for renal damage. Similarly, imaging costs are notoriously variable; thus, the relative cost of each approach may differ from one institution or region to another.

A recent refinement of the top-down algorithm would avoid some of these issues. Preda and colleagues found serum C reactive protein (CRP) $\geq$70 mg/l and a renal anteroposterior diameter $\geq$10 mm to be highly predictive of renal damage after 1 yr ($c = 0.81$). Using these criteria to determine which children merited post-UTI imaging would have kept 126 infants (47%) from undergoing acute DMSA and 161 (60%) from undergoing VCUG while missing 9 infants (13%) with renal scarring and 4 (15%) with dilating VUR [55].

Several reports have recently shown promising results using serum procalcitonin levels to detect children with APN-related renal damage on DMSA scan [56], including a recent prospective study showing superior results with procalcitonin when compared with erythrocyte sedimentation rate and CRP [57]. Others have reported success using serum procalcitonin levels to identify patients with significant VUR and renal damage in an effort to reduce VCUG use [58]. Such advances with the use of biomarkers to identify children at risk for renal damage and/or high-grade VUR in patients with febrile UTI could help to determine who would benefit from further evaluation and treatment. Similarly, some authors advocate use of ^{51}Cr-ethylenediaminetetraacetic acid to estimate the function of each renal unit in addition to DMSA renal scans [59], while others recommend magnetic resonance urography to evaluate for renal hypotrophy [60].

Importantly, ESPR guidelines state that "obviating all imaging in UTI is dangerous" and recommend that, at a minimum, RBUS should be performed in children after a febrile UTI [26]. In contrast, NICE guidelines note that "routine imaging of all children after a first UTI is inappropriate" [24]. NICE recommends RBUS only for atypical or recurrent UTI or for children <6 mo of age. DMSA (performed 4–6 mo after UTI resolution) is recommended only in children <3 yr of age with atypical or recurrent UTI.

Although one study has noted high predictive values for these guidelines [61], others have reported serious problems. Lytzen et al. recently reviewed a series of 96 consecutive children presenting with their first episode of APN. Of nine children with grade III–V VUR, five would have been missed using NICE guidelines, four of whom ultimately underwent surgery [62]. Another case-control study examined the NICE assertion that clinical symptomatology alone could be used to predict future renal scarring. Based on a review of 191 children presenting with UTI, the authors found a weak correlation ($r^2 = 0.03$) between symptoms such as vomiting, anorexia, or malaise and no significant correlation for gender, age, fever, or need for hospitalization ($p > 0.05$ for all) [63].

Ultimately, the guidelines for initial management of VUR and UTI are heterogeneous. VUR is neither necessary nor sufficient for developing APN, but VUR is associated with an increased likelihood (odds ratio: 2.8) of renal scarring on late DMSA scan [25]. Although compelling data and sound logical reasoning can be provided for both arguments, there is as yet no consensus as to whether a kidney- or bladder-centric approach is preferable for initial imaging of VUR.

3.2. Screening for vesicoureteral reflux in asymptomatic children

3.2.1. Screening for vesicoureteral reflux in siblings and children of vesicoureteral reflux patients

VUR is a familial polygenic disorder with an autosomal dominant type mode of transmission [64]. Whereas VUR is thought to be present in 1% of the general pediatric population, the average prevalence of VUR is 27% among siblings of children with VUR and 36% among offspring of parents with VUR [27].

Because of this increased likelihood of VUR, the EAU recommends screening asymptomatic siblings of VUR patients based on the assumption that if sibling VUR is diagnosed early, measures can be implemented to prevent future UTI and renal scarring [29,65,66]. AUA recommendations are similar: Parents should be informed about the increased risk of VUR, and RBUS can be offered to siblings (particularly those who are not yet toilet-trained), although the ability of RBUS to detect VUR is limited. If RBUS reveals any abnormality, VCUG is recommended. If parents choose not to screen, then prompt treatment of febrile episodes or presumptive UTI is required, followed by a complete investigation for VUR [27].

Both the EAU and AUA guidelines note that the effectiveness of CAP in preventing febrile UTI has been questioned [67,68], implying that the identification of VUR may not be worthwhile if future renal sequelae cannot be prevented. Unfortunately, there is relatively little observational data on this topic [65,69], and an adequate RCT of sibling screening would be difficult to perform [70]. Assuming that CAP is highly effective at preventing renal damage, >30 asymptomatic siblings would need to be screened at a cost of US $56 000 to prevent a single febrile UTI. Assuming CAP to be ineffective, >430 siblings would need to be screened at a cost of US $820 000 [71]. A prospective trial on this topic has been proposed in the United Kingdom [72]; if well designed and adequately powered, such a trial would almost certainly provide the best evidence yet as to whether to screen asymptomatic siblings and offspring of VUR patients.

There are little high-level data on screening asymptomatic siblings or offspring of VUR patients. Analyses of existing data suggest that this practice would be costly and may not be effective against reducing the risk of UTI and renal scarring, but these analyses are subject to the flaws inherent in the literature upon which they are based.

3.2.2. Screening for vesicoureteral reflux in children with prenatal hydronephrosis

During fetal development, VUR may manifest as prenatal hydronephrosis (PNH). This possibility has led some authors to advocate screening children with PNH for VUR. As with screening of siblings and offspring of VUR patients, the goal is to prevent renal damage by instituting CAP or other treatments early. As with sibling screening, this approach is subject to questions regarding treatment effectiveness. On prenatal ultrasound, a variable degree of hydronephrosis or hydroureter may suggest VUR, although no fetal findings can reliably diagnose VUR. The incidence of reflux appears to increase with the degree of dilation; on average, 15.2% (95% confidence interval [CI], 10.9–20.7) of children with mild to moderate PNH will be found to have VUR regardless of postnatal RBUS findings [25]. However, the degree of dilation does not correlate with the grade of VUR [30]. Those with VUR are relatively evenly divided among VUR grades, with roughly one-third having grades I–II, one-third grade III, and one-third grades IV–V. Therefore, both the SFU and the AUA recommend VCUG for children with SFU grade III–IV PNH, hydroureter, or an abnormal bladder on fetal ultrasound [25,30].

3.3. Treatment options for children with vesicoureteral reflux

The consensus management goals for children with VUR are to prevent febrile UTI, prevent renal injury, and minimize patient morbidity [25,29]. Ideally, treatment choice should be evidence based and may vary depending on each child's gender, age, reflux grade, history of recurrent UTI, renal function, and associated bladder/bowel dysfunction (BBD) in addition to parental and provider experience and preference (Table 2). In general, VUR treatment can be either conservative or interventional and may include CAP, EI, or ureteroneocystostomy.

3.3.1. Antibiotic prophylaxis

CAP was widely viewed as standard initial management of most children with VUR until recent studies raised doubts regarding its effectiveness [15–19]. Many children with VUR will spontaneously resolve with age, particularly those with low-grade reflux [5,73,74]. The majority of children with low-grade VUR are not at risk for recurrent episodes of APN or renal scarring. Early studies found that CAP effectively reduced the risk of febrile UTI while allowing time for resolution to occur [75]. More recent studies have

Table 2 – Clinical guidelines for management of children with vesicoureteral reflux

Organization	Patient age, yr	LUTS	Febrile UTI	VUR grade	Initial management	Indication for surgery
EAU/ESPU [29]	<1	N/A	No	I–III	Observation	–
	<1	N/A	No	IV–V	CAP	Breakthrough UTI
	<1	N/A	Yes	All	CAP	Breakthrough UTI
	1–5	No	Either	All	CAP	Persistent VUR, breakthrough UTI
	1–5	Yes	Yes	I–III	Treat BBD, CAP	Persistent VUR, breakthrough UTI
	1–5	Yes	Yes	IV–V	Treat BBD, CAP vs surgery	Persistent VUR, breakthrough UTI
	>5	No	No	All	CAP	Persistent VUR, breakthrough UTI
	>5	Either	Yes	All	Treat BBD if present, CAP vs surgery	Persistent VUR, breakthrough UTI
AUA [25]	<1	N/A	No	I–II	Observation or CAP, consider circumcision in boys	Breakthrough UTI
	<1	N/A	No	III–V	CAP, consider circumcision in boys	Breakthrough UTI
	<1	N/A	Yes	All	CAP, consider circumcision in boys	Breakthrough UTI
	>1	Yes	Both	All	Treat BBD, CAP	Initial vs after breakthrough UTI
	>1	No	Both	All	Consider CAP (CAP recommended if renal scar, recurrent UTI)	Initial vs after breakthrough UTI

LUTS = lower urinary tract symptoms; UTI = urinary tract infection; VUR = vesicoureteral reflux; EAU = European Association of Urology; ESPU = European Society for Pediatric Urology; N/A = not applicable; CAP = continuous antibiotic prophylaxis; BBD = bladder/bowel dysfunction; AUA = American Urological Association.

cast doubt on this conclusion, however, while simultaneously raising concerns of antibiotic resistance [15–19]. The effectiveness of CAP is likely reduced by poor compliance, estimated to be only 40% in multiple studies [76,77].

In the PRIVENT study, 576 children were randomized to receive trimethoprim-sulfamethoxazole or placebo. Investigators found a 6% absolute reduction in UTI in those receiving prophylaxis (39% relative reduction; 95% CI, 7–60), independent of patient gender, age, and VUR status [21], although there is some question whether the study was adequately powered to evaluate VUR grade [78]. Similarly, investigators in the Swedish Reflux Trial randomized 203 children with grade III–IV VUR and a history of UTI to CAP, EI, or surveillance off antibiotics. Children who did not receive CAP were 3 times more likely to develop a febrile UTI than those maintained on CAP (57% vs 19%; $p = 0.0002$). This effect was most pronounced in girls >1 yr of age with grade III–V VUR and least pronounced in boys [20]. A recent Cochrane review compiled data from 20 randomized trials (2324 children total) of CAP. Unfortunately, the methodologic quality of these studies varied significantly, with 75% of included studies noted to be at high risk of detection bias and 30% at high risk of attrition or reporting bias. This heterogeneity "made drawing firm conclusions challenging" [14]. Nevertheless, long-term CAP, averaged across all included studies, did not appear to significantly reduce the risk of febrile UTI in children with VUR. Similarly, the AAP recently performed a meta-analysis of CAP to prevent febrile UTI in 2- to 24-mo-old children with VUR, including the PRIVENT and Swedish trials; no statistically significant benefit was noted for grade I–IV VUR ($p > 0.3$ for all) [28].

The role of CAP is less clear in view of data demonstrating that it is less effective at preventing recurrent UTI than previously assumed. Forthcoming studies (particularly RIVUR) will hopefully better define its role. Whether subgroups of patients who may benefit more from CAP will be identified remains to be determined.

3.3.2. *Treatment of bowel/bladder dysfunction*

An important aspect of VUR management, including CAP, is treatment of BBD if present, as BBD is associated with an increased probability of recurrent UTI and a reduced probability of VUR resolution [79,80]. There are insufficient data to recommend a general rather than an individualized treatment regimen for BBD, but possible options include behavioral therapy, biofeedback (particularly for school-age children), anticholinergic medications, alpha blockade, and constipation management [25].

3.3.3. *Endoscopic injection*

EI of periureteral bulking agents was first described by Matouschek in 1981 [9] and later popularized by Puri and O'Donnell [10]. The use of EI increased following the approval of dextranomer/hyaluronic acid (Dx/HA) copolymer for use in the United States after 2001. EI use appears now to have plateaued, although per-patient injected volumes of Dx/HA have steadily increased [81]. However, these increased numbers of EI have not resulted in decreased numbers of ureteroneocystostomies [82,83], indicating a shift in surgical indications in some centers or regions [84].

Meta-analyses demonstrate that, on average, 77% of ureters injected with Dx/HA are VUR-free 3 mo after injection, similar to other biomaterials (Table 3) [85,86]. However, centers have reported tremendously variable cure rates (50–94%) [87,88]. EI studies are plagued by consistently low reporting quality, as evidenced by their extremely high study heterogeneity ($I^2 = 87\%$; 95% CI, 84–90) [86]. This variability indicates substantial between-study differences in methodology and study design. The reasons behind these differences are myriad and include differences in patient selection in addition to surgeon or technical factors [86]. Length of follow-up in particular has a tremendous impact on success rates. Although some groups have reported high (>90%) success rates after a follow-up period of only 4–6 wk [88], studies with longer follow-up suggest that these results may not be durable [89–92]. In the Swedish Reflux Trial, 20% of previously successfully

Table 3 – Cure rates of vesicoureteral reflux treatments: pooled results of systematic reviews

Grade	Spontaneous resolution at 1 yr* [5]		Spontaneous resolution at 5 yr* [5]		Open ureteral reimplant [5]		EI with Dx/HA [86]	
	No. of treated ureters	Cure rate, %	No. of treated ureters	Cure rate, %	No. of treated ureters	Cure rate, %	No. of treated ureters	Cure rate, %
I	25	39	25	92	109	99	164	89
II	375	28	375	81	882	99	1399	83
III	327	10	327	42	1010	98	2354	71
IV	220	6	220	16	392	99	1109	59
V	–	–	–	–	192	81	123	62
Weighted average: all grades	947	17	947	53	2585	97	5149	72

EI = endoscopic injection; Dx/HA = dextranomer/hyaluronic acid.
* Resolution rates are weighted, per-ureter averages.

treated children recurred after 2 yr of follow-up, despite relatively high success rates (86%) [89]. Other studies have shown that contributing factors to delayed VUR recurrence in patients treated with EI include a history of BBD, multiple preoperative UTIs, and abnormal DMSA scan findings [93,94]. Despite similar infection rates between patients receiving prophylaxis and those undergoing Dx/HA injection in the Swedish Reflux Trial (19% vs 23%; $p = 0.8$) [20], there was a trend toward increased renal scarring among Dx/HA patients (6% vs 12%; $p = 0.055$) [95]. Both infection and scarring rates in the Dx/HA patients were similar to patients who received no treatment. Given the variability of reported EI effectiveness, it is perhaps not surprising that estimates of its cost-effectiveness are similarly varied [96–100].

Finally, there is significant disagreement as to what constitutes "successful" endoscopic treatment. In many European studies, the presence of grade I–II VUR after injection is considered successful [89,90,101]. In North American studies, injection success is typically defined as the absence of VUR [87,93].

EI remains a useful tool in some children who are being considered for surgery, although outcomes may not be durable. The methodology and reporting of many EI studies require improvement.

3.3.4. *Ureteroneocystostomy*

Ureteroneocystostomy has been consistently shown to have resolution rates in excess of 95% (Table 3) and to reduce a child's risk of febrile UTI by 57% [5], although it is estimated that eight children would require surgical and antibiotic treatment to prevent one febrile UTI [14]. Research has therefore been directed toward minimizing morbidity rather than improving effectiveness, including improved use of pre- and postoperative care pathways [102], improved intra- and postoperative analgesia [103,104], decreased incision size [105,106], and decreased catheter use [107].

In addition to open ureteroneocystostomy, significant advances have been made in laparoscopic [108–110] and robotic [111,112] techniques. These techniques have now been shown to be safe and effective in preliminary studies. Interestingly, the benefits of these minimally invasive options are not dramatically superior to open approaches [112,113], perhaps reflecting improvements in surgical technique and postoperative management in open ureteroneocystostomy.

Ureteroneocystostomy remains a highly effective option for those patients for whom immediate VUR resolution would be beneficial. Recent advances have significantly reduced, but not eliminated, patient morbidity.

3.4. *Ongoing research and future opportunities*

There is much to look forward to in forthcoming VUR research (Table 4). Perhaps most prominently, the multicenter, double-blind, placebo-controlled RIVUR study has recently completed accrual of >600 children with VUR. Study participants were randomized to receive a 2-yr course of either antibiotic prophylaxis or placebo; follow-up data will be collected on participants through 2013. Study end points include UTI recurrence, renal scarring, and antimicrobial resistance in addition to patient quality of life, compliance with therapy, resource utilization, and change in VUR status over the 2-yr follow-up period [114].

Although patient accrual in RIVUR was successful, VUR researchers face multiple challenges in recruiting patients to participate in clinical research. It is inherently difficult to randomize patients—particularly children—to surgical treatments, as evidenced by the low randomization rate in the RIVUR study. This selection process may ultimately affect trial results. Newer study designs, such as comparative effectiveness research studies or novel randomized trial designs, may minimize or circumvent this issue [115]. Recent studies of other problematic surgical subjects (eg, localized prostate cancer [116]) imply that these approaches could be used successfully in pediatric urology, as well.

Although clinical research can refine management options for children with VUR, it seems clear that existing diagnostic and therapeutic options could be significantly improved. Ongoing translational and basic science research may accomplish this, such as the application of noninvasive microwave energy to detect thermal evidence of VUR in the kidney after warming urine in the bladder [117]. In addition, improved identification of (and risk stratification for) children predisposed to VUR-related pathology is sorely needed, such as a new VUR classification system that would

Table 4 – Ongoing or proposed vesicoureteral clinical research trials

Study title (clinicaltrials.gov identifier)	Setting	Planned enrollment	Design	Description/objectives
RIVUR (NCT00405704)	Multicenter, USA	600	Placebo-controlled, double-blind randomized trial	Compare TMP-SMX and placebo in children with VUR over 2-yr follow-up
Antibiotic Prophylaxis in Children with Pyelonephritis (NCT00752375)	University of Alberta, Canada	140	Placebo-controlled, double-blind randomized trial	Compare TMP-SMX and placebo in children with pyelonephritis over 5-year follow-up
Bacterial and Host Genetic Risk Factors in Acute Pyelonephritis (NCT01137929)	Children's National Medical Center, USA	240	Prospective case-control trial	Define the relationships between clinical aspects of UTI, especially host immune response and causative microbes
Prospective Pediatric Vesicoureteral Reflux Surgery Database (NCT01373385)	Connecticut Children's Medical Center, USA	200	Prospective cohort	Collect performance and outcomes data for the surgical treatment of VUR at a single center

RIVUR = Randomized Intervention in Vesico-Ureteral Reflux; TMP-SMX = trimethoprim-sulfamethoxazole; VUR = vesicoureteral reflux; UTI = urinary tract infection.

account for both radiographic and clinical features. Biomarker discovery (such as procalcitonin) and system-level research (such as genomics or proteomics) remain critical research targets [118,119].

4. Conclusions

The present literature is marked by controversy and divergent guidelines regarding VUR imaging, screening, and treatment, although there are multiple areas of consensus. VUR is neither necessary nor sufficient to cause APN and renal scarring in children, but compelling evidence shows that VUR remains strongly associated with renal damage. As urologists, it is incumbent upon us to better define the evidence surrounding VUR practice patterns. High-value target areas for future research include improved identification of children who are (and who are not) at risk for VUR-related renal morbidity, improved stratification tools for determining which children would benefit most from evaluation and which VUR treatment option would be best for each child, and improved reporting of long-term outcomes of VUR treatments.

Author contributions: Jonathan C. Routh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Routh, Bogaert.
Analysis and interpretation of data: Routh, Bogaert, Kaefer, Manzoni, Park, Retik, Rushton, Snodgrass, Wilcox.
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