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Primary aims in the diagnosis and management of vesicoureteral reflux (VUR):

1. Reduce recurrent febrile urinary tract infection (fUTI).
2. Prevent acquired renal damage.

Summary of evidence for these aims:

Children with VUR have been assumed to have high risk for renal scarring and recurrent fUTI, justifying therapy in most patients.

However:

- RCTs indicate only approximately one-third of patients with VUR will have recurrent UTI within 2 years of diagnosis
- Acquired renal scarring occurs in approximately 15 % of children with VUR after fUTI.
- If DMSA scan for renal scar is negative, risk subsequent fUTI will cause renal damage is ≤ 10 %.
- No randomized controlled trial (RCT) has been done to determine if VUR therapy (medical or surgical) decreases additional acquired renal damage in children with renal scar at presentation.

- Antibiotic prophylaxis is no more effective than placebo to prevent recurrent UTI in children 1–24 months of age with grades 1–4 VUR.
- There are no data regarding benefit of antibiotic prophylaxis in children >2 years of age with VUR, with VUR and no history of UTI, with grade 5 VUR, or with recurrent UTI.
- Surgical correction of VUR (reimplantation or endoscopic injection) reduces recurrent fUTI.
- Identification and treatment of voiding dysfunction in children with VUR has not been clearly demonstrated to improve resolution or reduce fUTI.

The two indications to diagnose and treat VUR are to decrease likelihood for recurrent fUTI and renal scarring. The association of VUR to fUTI and renal scarring has prompted investigations not only to diagnose VUR after UTI, but also in siblings or offspring of patients with VUR, and in newborns with prenatal hydronephrosis. However, recent prospective trials and observational studies indicate most children with VUR will not have frequently recurrent infections after their initial one, and most will not develop renal scarring. Furthermore, these studies also challenge the foundation of VUR management, questioning efficacy of continuous antibiotic prophylaxis to prevent recurrent UTI in children with VUR.

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VUR Prevalence

After Febrile UTI

VUR is diagnosed in one-third or fewer of patients less than approximately 2 years of age following fUTI. Grades 1–3 account for over 75 % of cases, and are equally distributed between genders, while grades 4 and 5 are more common in males.

Several prospective studies have reported VUR incidence after first known symptomatic UTI:

- 302 children (33 boys) ages 1–24 months underwent VCUG after first fUTI. VUR occurred in 117 (39 %), grade 1 in 25, grade 2 in 42, grade 3 in 45, grade 4 in 5, and grade 5 in 0 children. Therefore, 96 % of VUR cases were grades 1–3. Note the small percentage of males in the study, who are more likely than females to have the higher VUR grades (Hoberman et al. 2003).
- 297 consecutive children (169 boys) under age 5 years with first symptomatic UTI (fUTI in 242) reported reflux in 28 %, but did not state the grades (Craig et al. 1998).
- 209 children with first symptomatic UTI at median age 10 months (0.2–204) had 53 (25 %) cases of VUR. Of these, 45 (85 %) were grades 1–3, while 8 (15 %) were grades 4 and 5 (gender not stated) (Ismaili et al. 2011).
- 72 term neonates 0–28 days of age with symptomatic UTI (fever, vomiting, poor feeding, failure to thrive) underwent VCUG, with VUR reported by renal units occurring in 22 % found equally in males and females. Of 144 renal units, there were grades 1 and 2 in 13 (9 %), grade 3 in 10 (7 %), and grades 4 and 5 in 8 (5.5 %). Grades 4 and 5, which accounted for 25 % of detected VUR, were found only in boys (Siomou et al. 2009).

Sibling and Offspring Screening

Siblings and offspring of affected patients have similar prevalence of VUR, approximately one-third of those screened.

Most detected VUR is low grade, with approximately 10 children per 100 screened having grades 3–5.

Prevalence of VUR decreases with age.

Meta-analysis of 22 published articles by the AUA Reflux Guidelines panel found data regarding VUR in siblings ($n=2,957$) and offspring ($n=244$), reporting the following:

- 100 % concordance in identical twins.
- 35–50 % prevalence in fraternal twins.
- Overall incidence was 27.4 (95 % CI 2.9–51.9)/100 screened siblings.
- Detected VUR grade was reported as “low grade” 1 and 2 vs. “high grade” 3–5. Most was low grade, with a mean prevalence of grades 3–5 in 9.8 (95 % CI 5.3–17.4)/100 siblings screened.
- Males and females were equally affected.
- Incidence in offspring was 35.7 (95 % CI 16.4–61)/100 screened.

Likelihood for VUR in screened persons decreased with age at a rate of 4 % per year (Skoog et al. 2010).

Prenatal Hydronephrosis

VUR is found in 16 % of infants diagnosed with prenatal hydronephrosis.

Prevalence is not influenced by extent of prenatal dilation, and it remains unchanged even if postnatal ultrasound (US) is normal.

Two-thirds of detected VUR are grades 1–3.

There are no data to determine if antibiotic prophylaxis to prevent first UTI in neonates with VUR is more effective than no treatment.

Meta-analysis by the AUA Reflux Guidelines panel to determine prevalence of VUR in newborns with prenatal HN included 34 studies in which the mean percentage of screened patients was 78 % (11–100 %), reporting the following:

- VUR occurred in an average of 16 % (7–35 %) with cystography.
- Grade distribution was approximately one-third each for grades 1–2, 3, and 4–5.
- VUR occurred in the non-dilated kidney in 25 % of cases.
- Prevalence was 18 % even if postnatal US was negative for HN.

- Extent of prenatal dilation did not predict likelihood for postnatal VUR.

Relative risk for UTI posed by this VUR could not be assessed from literature review, nor could possible impact, if any, of antibiotic prophylaxis (Skoog et al. 2010).

Likelihood for Recurrent fUTI

Less than one-third of children diagnosed with VUR after first fUTI receiving no therapy will have a second fUTI in the following 2 years.

Of those with recurrent infection, most will have a single recurrence, with less than 10 % of patients having three or more recurrences within 1–2 years.

The following is a summary of recurrent fUTI rates in patients with VUR from prospective studies:

- 225 children (69 boys, “most” not circumcised) ages 1 month to 3 years with first fUTI found to have grades 1–3 VUR were followed for 18 months. Recurrent fUTI developed in 32 (14 %) (Roussey-Kesler et al. 2008).
- 100 children (48 boys) <30 months of age with first fUTI and found to have VUR grades 2–4 were followed for 2 years. Recurrent fUTI occurred in 33 %, one episode in 11, two episodes in 3, and three or more episodes in 2 (Pennesi et al. 2008).
- 87 children (22 boys) 3 months to 12 years of age with grades 1–3 VUR were enrolled after fUTI (number of UTIs prior to enrollment was not stated). Recurrent fUTI occurred in 8 (9 %) during 1-year follow-up (Garin et al. 2006).
- 68 children (26 boys) ages 1–2 years with grades 3 and 4 VUR were observed without treatment for 2 years. Number of fUTIs before enrollment was not stated. Recurrent fUTI developed in 25(37 %) (Brandstrom et al. 2010).

Renal Scarring

VUR increases likelihood of renal scar by approximately 2.5 times, with increasing risk associated with increasing reflux grade, especially grades 4 and 5.

Presumed congenital reflux nephropathy was found in 4 % and focal scars in 19 % of referred patients with VUR in one study.

Meta-analysis to determine risk for renal scarring in children with UTI included 33 studies and reported scar by follow-up DMSA scan in 15 % (95 % CI 11–18). VUR had significantly increased relative risk for scar (RR 2.6 [95 % CI 1.7–3.9]), based on four studies (Shaikh et al. 2010).

A prospective study of 565 consecutive children referred for urologic assessment after fUTI and/or VUR diagnosis included DMSA scintigraphy ≥ 3 months after infection (mean 7.4 months; median 4 months), if present. Presumed congenital reflux nephropathy (≤ 44 % ipsilateral function and no cortical defects) was found in 24 (4 %), while focal cortical defects likely representing scars were found in 84/541 (15.5 %) remaining study patients. Of 340 patients with VUR, excluding those with congenital nephropathy, 65 (19 %) had focal scar. This comprised 12 % of patients with grades 1–2, 15 % with grade 3, and 50 % for grades 4–5. The OR for focal DMSA abnormalities by VUR grade were grade 1, 3.94 (95 % CI 1.05–14.85); grade 2, 3.12 (95 % CI 1.35–7.21); grade 3, 3.93 (95 % CI 1.68–9.22); grade 4, 28.91 (95 % CI 10.73–77.86); and grade 5, 77.37 (95 % CI 16.62–360.20) (see Table 1.2) (Snodgrass et al. 2012).

New Renal Scars After Prior Negative DMSA

Our review found one RCT and one retrospective review that reported 11 and 3 % of patients with VUR and a prior negative DMSA scan developed renal scar with recurrent UTI.

The IRS reported 15 % of patients and 4 % of kidneys with normal DMSA at entry developed focal defects and/or renal function decrease, but related events (fUTI, obstruction after reimplantation) were not specifically described for these children versus those with abnormal DMSA at entry.

The European branch of the IRS obtained DMSA at entry and again during follow-up at a duration of 5 years (timing of second scan not clearly stated). There were 306 children, median age 3.5 years, with DMSA studies completed and/or of sufficient

quality for review in 287. All had UTI before entry, and initial DMSA was done afterwards at <2 months in 6 %, between 2 and 6 months in 40 %, and at >6 months in 54 %. During follow-up, 95 % of DMSA were obtained >6 months after last UTI. Entry DMSA was normal in 52 patients, and during follow-up 8 (15 %) showed deterioration; of 246 normal kidneys at entry, 11 (4 %) showed deterioration. There was no difference in changes based on randomization to medical versus surgical therapy. Details regarding these patients with initially normal scans who developed cortical defects or renal function loss were not specifically described. Overall DMSA changes occurred in 48 children, including 9 who developed obstruction after reimplantation and 32 stated to not have UTI during management (Piepsz et al. 1998).

The Swedish reflux trial included 203 patients with mean age 1.8 years (1–2) with grades 3 and 4 VUR. Number of fUTI prior to entry was not stated, but baseline DMSA was positive in 124 (61 %). New defects in those with negative DMSA occurred in 9/79 (11 %). Timing of DMSA and number of recurrent UTIs were not stated (Brandstrom et al. 2010).

A retrospective analysis of 138 children (53 boys) with VUR grades 1–5 included acute DMSA with subsequent DMSA 4–6 months later for abnormal findings, and another late DMSA 4–6 months after recurrent UTI. Recurrences developed in 118, but only 26 were described as fUTI and only 16 involved more than one recurrent episode. Of these, 2/71 (3 %) without scar during first evaluation were found to have new scar formation (Soylu et al. 2008).

Natural History

VUR may spontaneously resolve, with likelihood influenced by grade, laterality (unilateral versus bilateral), and patient age at diagnosis.

Initially diagnosed unilateral VUR is found in up to 20 % of cases to have contralateral VUR on subsequent cystography.

Spontaneous Resolution

Graphs summarizing VUR resolution during medical therapy were published by the first AUA

Reflux Guidelines panel. These 10 resolution curves for grades 1–4 were constructed using data from three articles that comprised a total of 587 patients, of which 250 (43 %) had grade 2 (Elder et al. 1997). Subgroups with included patient numbers and percent chance for resolution in 1–5 years are found in Table 2.1.

Nomograms for VUR resolution were also constructed from a longitudinal database maintained from 1998 and analyzed in 2006 containing 2,462 children. Annual cystography was done following diagnosis, with resolution defined as one negative study. Spontaneous resolution occurred in 51 % during mean follow-up 1.95 ± 1.37 years: 72 %, grade 1; 61 %, grade 2; 49 %, grade 3; and 32 %, grades 4–5. Another 23 % had ongoing VUR at mean follow-up 2.6 ± 1.6 years, and the remaining 26 % underwent surgery at 2.3 ± 1.6 years. Multivariable analysis showed increased spontaneous resolution for the following:

- Age <1 year (HR 1.31 [95 % CI 1.16–1.48])
- Prenatal HN of sibling VUR (HR 1.24 [95 % CI 1.08–1.42])
- Single ureter (vs. duplication) (HR 1.55 [95 % CI 1.24–1.9])
- Male gender/unilateral female (HR 1.42 [95 % CI 1.26–1.59])

As a group, males and those females with unilateral VUR resolved faster than females with bilateral VUR (Estrada et al. 2009)

Internet-based calculators have been developed to predict spontaneous resolution in individual patients based on a variety of clinical data points. Each was created using different methods based upon retrospective data, including a logistic regression model, a neural network, and literature meta-analysis. A study inputting identical theoretic patient characteristics into each reported statistically significantly different predictions for spontaneous resolution (Routh et al. 2010).

New Contralateral VUR

A retrospective review was done in 167 children (33 boys) diagnosed at mean age 55 months (2–169) with unilateral VUR from 1986 to 2004. Two-cycle VCUGs were performed. All patients

Table 2.1 Percent chance of VUR resolution^a

Risk category (age in months)(number of patients on which estimates are based)	Percent chance (95 % confidence interval)				
	1 year	2 years	3 years	4 years	5 years
Grade I ^b (n = 15)	39.3 (24.6–51.1)	63.1 (43.2–76.1)	77.6 (57.2–88.3)	86.4 (67.7–94.3)	91.8 (75.7–97.2)
Grade II ^b (n = 250)	28 (24.1–31.7)	48.1 (42.3–53.4)	62.7 (56.2–68.1)	73.1 (66.8–78.2)	80.6 (74.8–85.1)
Grade III, unilateral, age 0–24 (n = 27)	21.4 (10.8–30.8)	38.2 (20.4–52.1)	51.5 (29–66.8)	61.9 (36.6–77.1)	70 (43.5–84.1)
Grade III, unilateral, age 25–60 (n = 27)	13.4 (4.6–21.4)	25 (8.9–38.3)	35.1 (13.1–51.5)	43.8 (17.1–61.9)	51.3 (20.9–70.1)
Grade III, unilateral, age 61–120 (n = 15)	10.8 (3.5–17.5)	20.5 (6.9–32)	29.1 (10.2–43.9)	36.7 (13.4–53.8)	43.6 (16.5–61.9)
Grade III, bilateral, age 0–24 (n = 62)	12.7 (7–18.1)	23.8 (13.5–32.9)	33.5 (19.5–45)	41.9 (25.1–55)	49.3 (30.3–63.1)
Grade III, bilateral, age 25–60 (n = 53)	7 (3.1–10.8)	13.5 (6.1–20.4)	19.6 (9–28.9)	25.2 (11.8–36.6)	30.5 (14.6–43.4)
Grade III, bilateral, age 61–120 (n = 14)	2.6 (0.7–4.5)	5.2 (1.4–8.8)	7.7 (2.1–13)	10.1 (2.8–16.9)	12.5 (3.5–20.7)
Grade IV, unilateral ^c (n = 28)	16.1 (8.5–23.1)	29.7 (16.4–40.8)	41 (23.5–54.5)	50.5 (30–65)	58.5 (36–73.1)
Grade IV, bilateral ^c (n = 96)	4.5 (1–7.9)	6.4 (2–15.1)	7.8 (3–21.8)	8.9 (4–28)	9.9 (4.9–33.7)

^aReproduced with permission from Jack S. Elder, MD; Craig Andrew Peters, MD; Billy S. Arant, Jr., MD; David H. Ewalt, MD; Charles E. Hawtrey, MD; Richard S. Hurwitz, MD; Thomas S. Parrott, MD; Howard M. Snyder, III, MD; Robert A. Weiss, MD. AUA Pediatric Vesicoureteral Reflux Clinical Guidelines Panel: The Management of Primary Vesicoureteral Reflux in Children. American Urological Association Education and Research, Inc., © 1997. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/archived-guidelines/vesi_reflux07.pdf. The yearly rate of reflux resolution remains constant for each group

^bNo difference shown by age or laterality (unilateral/bilateral); therefore, these categories were combined

^cEstimates only apply to the time of diagnosis and are not age-specific

had at least two cystograms, with 84 having three to seven studies. Contralateral VUR not seen on the initial VCUG occurred in 33 (21 %) in patients with a mean 3.5 ± 1.4 cystograms. This VUR was grade 1 in 4, 2 in 18, 3 in 9, and 4 in 1 patient. Variables analyzed included gender, side, age, VUR grade, and voiding dysfunction. Of these, only higher VUR grade was predictive, with contralateral VUR found in 12/91 (13 %) of grades 1–2 vs. 21/62 (34 %) with grades 3–5, $p=0.006$ (Barroso et al. 2008).

Voiding Dysfunction

Few studies report impact of treatment for voiding dysfunction on VUR outcomes.

Our review found only one retrospective analysis stating breakthrough UTI was significantly more likely, despite AC in females with VUR and urge syndrome versus those without voiding dysfunction.

One report found no difference in VUR resolution at 3 years in patients with versus without detrusor instability.

Two others reported spontaneous resolution in approximately 60 % of ureters with mostly grades 1 and 2 VUR in 6–12 months with biofeedback, but had no control groups.

The 2010 AUA Reflux Guidelines reported the following observations about VUR and bladder/bowel dysfunction (BBD):

- BBD increases risk for fUTI in children with VUR on antibiotic prophylaxis (44 % with BBD vs. 13 % without)
- Spontaneous VUR resolution is less at 24 months in children with BBD (31 % with vs. 61 % without)
- The rate of postoperative UTI after VUR surgery is greater with BBD (22 % vs. 5 %)

Despite these observations, the panel stated there are few data regarding the impact of treatment for BBD on VUR outcomes (Peters et al. 2010).

A retrospective study of females ages 3–10 years old with VUR systematically obtained history for voiding dysfunction, found in 36/94 (40 %) presenting after UTI (characterized as 1–2 or ≥ 3 in the preceding 12 months; febrile vs.

nonfebrile not stated). Those with symptoms of frequency, urgency, holding maneuvers, and/or diurnal incontinence for at least 6 months were treated with timed voiding and oxybutynin 2.5–5.0 mg/dose 3 times daily at 6-month intervals until symptoms did not recur off medication. All patients also received antibiotic prophylaxis. All were considered to have a satisfactory response to AC (not defined). Breakthrough UTI occurred in a total of 23/86 (27 %) with follow-up of 1 year, 18 (78 %) with urge syndrome. Breakthrough UTI was significantly more likely in females with treated urge syndrome versus those without symptoms, 18/42 (43 %) vs. 5/44 (11 %), $p=0.001$, despite similar age and VUR grades (Snodgrass 1998).

One-hundred one children, 67 % females, mean age 5 years (6 week to 15 year) with recurrent UTI (febrile vs. nonfebrile; number of infections not stated) underwent UD with fluoroscopy that identified VUR. Grades were 1 ($n=1$), 2 ($n=14$), 3 ($n=13$), 4 ($n=10$), and 5 ($n=1$). Of these patients, detrusor instability was diagnosed in 41 (41 %). Treatment comprised AC, and all children had antibiotic prophylaxis. Reimplantation was done as initial therapy in some patients and within 1 year in others (in ≤ 4 patients for recurrent UTI), leaving 30 patients (39 ureters) with detrusor instability with medical management and follow-up a mean of 3 years. Resolution occurred in 15/39 (38 %), vs. 27/57 (47 %) ureters in 42 patients with a stable bladder, $p=0.4$. UTI following treatment was not clearly described (Scholtmeijer and Nijman 1994).

Twenty-five females, mean age 9 years (6–10), with VUR and dysfunctional voiding underwent a mean of seven biofeedback sessions (2–20) weekly–biweekly with repeat VCUG 1 year later. VUR grade was 1 ($n=10$), 2 ($n=15$), 3 ($n=5$), and 4 ($n=1$). Resolution occurred in 17/31 (55 %) ureters. Correlation to dysfunctional voiding was not described, except to state that all children with resolved VUR had resolved or improved symptoms and decreased PVR from a mean 40–10 % voided volume (Palmer et al. 2002).

Seventy-eight children, 90 % females, mean age 9 years (5–14), were diagnosed with dysfunctional voiding (uroflow with pelvic floor EMG)

and VUR, which was grade 1 ($n=26$), 2 ($n=32$), 3 ($n=28$), and 4 ($n=12$). All received urotherapy (“proper toilet posture,” hydration, timed voiding) and biofeedback for a median 6 (2–14) sessions. At 6 months follow-up, subjective reduction in symptoms of $\geq 90\%$ was reported for diurnal incontinence in 70 % and frequency in 76 %, and normalization of uroflow patterns occurred in 80 %. VUR resolved in 63 % of affected renal units (96 and 81 % of grades 1 and 2, 36 % of grade 3, and 8 % of grade 4). UTI was not discussed (Kibar et al. 2007).

Impact of VUR on Pregnancy

There are limited data regarding pregnancy risks from uncorrected VUR.

One literature review reported the primary risk factor for pregnancy complications, including UTI, gestational hypertension, preeclampsia, or fetal morbidity, was renal scarring.

The first AUA Reflux Guidelines panel reviewed published literature on this subject and concluded available data were insufficient to determine actual risk of uncorrected VUR during pregnancy. They reviewed five studies that demonstrated renal insufficiency increased toxemia, preterm labor, fetal growth retardation, and fetal demise (Elder et al. 1997).

Literature review regarding impact of VUR on pregnancy identified 15 articles for inclusion, reporting the following:

- fUTI in pregnancy (four studies) ranged from 3 to 37 %; fUTI in patients with childhood ureteral reimplantation (two studies) occurred in 25/141 (18 %) and 5/77 (7 %).
- Hypertension in pregnancy (three studies) was not increased by history of VUR with no renal scarring; hypertension occurred in 31 and 42 % with renal scarring (extent of renal damage not described).
- Preeclampsia (five studies) was increased by renal scarring; two studies reported no increased preeclampsia without renal scarring in a total of 23 women.
- No study reported history of VUR impacted fetal outcomes; one reported 8/39 pregnancies

with renal scarring had low birth weight (Hollowell 2008).

Management

VUR management aims to reduce recurrent fUTI and renal scarring.

Historically, risk for fUTI and renal scar have been assumed present in all children with VUR, with management based on the general assumption that reflux should resolve or be surgically corrected, especially in girls.

Few studies specifically address impact of treatment on recurrent UTI and/or renal scarring.

Continuous Antibiotic Prophylaxis

Continuous antibiotic prophylaxis (CAP) has been routinely recommended in children with VUR while awaiting spontaneous reflux resolution.

Meta-analysis of six RCTs by the 2011 AAP UTI Guidelines panel concluded antibiotic prophylaxis is no more effective than no therapy to prevent recurrent fUTI in children 1–24 months of age with grades 1–4 VUR.

Overall fUTI recurrence was 19 % in 1–2 years, with increasing percentage recurrence with increasing VUR grade.

There are no data regarding efficacy of CAP to reduce recurrent fUTI in patients with grade 5 VUR.

There are no data to determine if antibiotic prophylaxis is effective to prevent initial fUTI in children with VUR detected by sibling or prenatal hydronephrosis screening.

There are no data to determine efficacy of antibiotic prophylaxis in patients presenting with recurrent UTI.

Meta-analysis was done on data provided by six RCTs to determine efficacy of CAP to prevent recurrent fUTI versus no treatment in infants 2–24 months of age with VUR. Findings are shown in Table 2.2. There was no benefit of CAP versus no treatment for any grade of VUR, based on a sample

Table 2.2 Recurrence of febrile UTI/pyelonephritis in infants 2–24 months of age with and without antimicrobial prophylaxis, according to grade of VUR^a

Reflux grade	Prophylaxis		No prophylaxis		<i>p</i>
	No. of recurrences	Total <i>n</i>	No. of recurrences	Total <i>n</i>	
None	7	210	11	163	0.15
I	2	37	2	35	1.00
II	11	133	10	124	0.95
III	31	140	40	145	0.29
IV	16	55	21	49	0.14

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size of 718 patients: 72, grade 1; 257, grade 2; 285, grade 3; and 104, grade 4. Recurrent fUTI occurred in 133 (19 %); percentage fUTI recurrences by grade were 6 %, grade 1; 8 %, grade 2; 25 %, grade 3; and 36 %, grade 4 (AAP 2011).

Compliance with drug therapy has been raised as a potential confounder in these data, specifically that patients assigned to antibiotic might not have taken the medication, which likely would be representative of clinical practice. Of these six RCTs:

- Craig et al. assessed adherence by counting pills and direct questioning during visits. Sixteen percent of study patients discontinued therapy by 3 months, and 31 % at 12 months, with no difference in placebo versus drug treatment groups.
- Montini et al. tested antibiotic activity in routine urine cultures, with 71 % positive in the drug treatment group.
- Penesi et al. reported 6/50 (12 %) did not take prophylaxis.
- Brandstrom et al. stated 2/67 (3 %) admitted to noncompliance.
- Garin et al. excluded patients who self-admitted to noncompliance.
- Roussley-Kessler et al. did not assess compliance.

The AAP review limited analysis of antibiotic prophylaxis to children <2 years of age with grades 0–4 VUR after one febrile UTI. Our review found no reports concerning antibiotic prophylaxis in other scenarios:

- Grade 5 VUR
- Children with VUR and no history of UTI
- Children with recurrent UTI at diagnosis

Surgical Correction of VUR: Primary Outcomes

The two desired outcomes from surgical VUR correction are reduction in fUTI and renal scarring.

One RCT demonstrated ureteral reimplantation in children with VUR grades 3 and 4 significantly decreased recurrent fUTI over antibiotic prophylaxis (8 % surgical vs. 22 % medical therapy).

Three studies reported that recurrent fUTI after endoscopic injection occurs in ≤ approximately 10 % of patients. Odds for recurrence were 8.5 times greater in patients having more than three versus one febrile infection within 1 year before injection.

Recurrent febrile UTI after initially successful Dx/HA injection is associated with recurrent VUR in approximately 50 % of cases. Cystography for febrile UTI after reimplantation has not been reported.

There are no RCTs demonstrating VUR correction reduces renal scarring.

Ureteral Reimplantation

The International Reflux Study randomized children less than 11 years of age with grades 3 and 4 VUR to either antibiotic prophylaxis or ureteral reimplantation (Politano-Leadbetter, Lich-Grigoir, Cohen, based on surgeon preference). The US arm comprised 62 patients, 24 with unilateral and 38 with bilateral VUR, while the

European arm had 151 patients, 33 with unilateral and 118 with bilateral reflux. While overall UTI rates were similar between medical and surgical patients, fUTI occurred significantly less often after reimplantation (22 % medical vs. 8–10 % surgical, RR 0.43[95 % CI 0.27–0.70]) (Wheeler et al. 2003).

The European arm of the IRS obtained DMSA at entry and during 5-year follow-up in 287 children median age 3.5 years with grades 3 or 4 VUR. Of these, 52 (18 %) were initially normal. Follow-up DMSA was considered to show deterioration (new or larger cortical defect and/or renal function decrease >3 %) in 48 (17 %) children, including 8 (15 %) initially normal. There was no difference in these changes between those treated medically or surgically (Piepsz et al. 1998).

One study reported preoperative and postoperative DMSA scan in 143 children (45 boys) with VUR undergoing ureteral reimplantation at median age 2 years (2.5 month to 14 years). Maximum grade was 2–5 in 18, 59, 27, and 4 %. Preoperative scintigraphy was obtained less than 3 months after last UTI in 31 % of cases and not documented in 12 %, while 10 % had no history of UTI. Interval from DMSA scan to surgery was a mean 1.4 months (1 day to 1.5 years). Preoperative DMSA findings included congenital reflux nephropathy in 12 (8 %) and at least one kidney had abnormal findings in 94 (72 %) of the remainder. Postoperative DMSA was obtained at median 3 years (1–9). Postoperative UTI was known to have occurred in 12 %. One male developed a cortical defect, but he had UTI after his preoperative DMSA and before reimplantation, and another postoperatively 3 weeks before the last DMSA, so designation as scar and timing of injury was uncertain. Two other patients had new scars: one male with no preoperative UTI but “a scarred kidney” had one UTI postoperatively, while one female with preoperative scarring had recurrent postoperative UTI and a new scar. Timing of last DMSA in relation to last UTI was not stated. Overall mean change in ipsilateral renal function was 2.5 %, with nine kidneys in nine children having a 13–48 % decrease. There was no mention of

postoperative UTI occurrence in these patients. UTIs were not characterized as febrile or not (Webster et al. 2000).

Another retrospective study found that preoperative and postoperative DMSA scans had been obtained in 74 children (45 boys) out of 223 undergoing reimplantation from 1985 to 1997. These scans had been done a median 2 months (10 day to 58 months) before and a median 19 months (5–44) after surgery. fUTI occurred in only two patients after operation. No new scars were diagnosed (Choi et al. 1999).

Endoscopic Injection

Meta-analysis of reported outcomes in 12 studies after endoscopic injection stated recurrent fUTI occurred in 0.75 % (95 % CI 0.18–3.09) of patients. Incidence and frequency of pre-injection fUTI were not described, nor was duration of post-injection follow-up (Elder et al. 2006).

One study comprising 167 children with initially successful Dx/HA injection involved chart review and phone calls to both parents and PCP to determine incidence of recurrent infection. At median follow-up of 32 months (7–53), 12 % had recurrent fUTI, of which half had recurrent VUR on subsequent cystography. Multivariable analysis showed the number of preoperative fUTIs within 1 year of injection predicted UTI recurrence:

- Two to three preoperative infections, OR 3 (95 % CI 1.1–8.2) for postoperative fUTI
- Three preoperative infections, OR 8.5 (95 % CI 3.3–22) for postoperative fUTI (Chi et al. 2008)

Another retrospective study included 100 patients mean age 3.8 ± 0.3 years (24 % boys) after successful Dx/HA injection followed a mean of 15 months. A fivefold reduction in UTIs/year (febrile vs. nonfebrile not stated) was noted, from a mean 0.68 ± 0.09 pre-injection to 0.12 ± 0.04 post-injection. Recurrent infection occurred in 13 %, of which half had recurrent VUR (Wadie et al. 2007).

A third retrospective analysis reported Dx/HA injection in 311 children (41 boys) at mean age 5.7 years, of which 253 had negative cycled

VCUG post-injection. During mean follow-up of 2.6 years, 7 (3 %) developed fUTI. VCUG was repeated in five, and each demonstrated recurrent VUR (Traxel et al. 2009).

Correction of VUR: Secondary Outcomes

Reimplantation: Reflux Resolution

Published literature reviews indicate initial success for ureteral reimplantation to correct VUR in ≥ 95 % of ureters on cystography performed ≤ 6 months postoperatively.

The International Reflux Study reported VUR resolution 6 months after surgery in 94 and 89 % of US and European arms, respectively.

The European arm reported recurrent VUR in 3 % of patients at 5-year cystography.

There are few other data regarding recurrent VUR after reimplantation in either symptomatic or asymptomatic children to verify common opinion that surgical success is durable in the long term.

The first AUA Reflux Guidelines panel reviewed 86 articles providing reimplantation outcomes (published between 1965 and 1994) in 6,472 patients and 8,563 ureters. It reported overall success was 95 % of patients, and >98 % of ureters for VUR grades 1–4 and 81 % for grade 5. Techniques reviewed and date of last cystography after surgery were not stated (Elder et al. 1997).

A review of published outcomes for case series involving at least 100 reimplanted ureters analyzed 19 articles and the authors' own data comprising 3,346 patients and 5,008 ureters. Techniques used included Cohen, Politano-Leadbetter, Glenn-Anderson, and Lich-Gregoir. Overall VUR resolution occurred in 99 % of ureters. Five series reported failed reimplantation in a total of 40/1,116 (4 %) ureters on initial postoperative cystography, with spontaneous resolution in 1–5 years in 34 (85 %) (Bisignani and Decter 1997).

The US arm of the International Reflux Study included surgery in 87 patients and 157 ureters with grade 3–4 VUR done using the Cohen technique in 52 %, Politano-Leadbetter in 28 %,

Glenn-Anderson in 10 % and "other modifications" in 9 % (of patients). VUR persisted in five (6 %) patients, ultimately resolving spontaneously in all but one case at a mean of 20 months after surgery. There were no obstructions from surgery (Duckett et al. 1992).

The European arm operated on 150 patients (36 boys) and 237 ureters, using Politano-Leadbetter in 55 %, Lich-Gregoir in 26 %, and Cohen in 18 % (of patients). Persistent VUR was found at 6 months cystography in 15 % of bilateral and 6 % of unilateral reimplanted children, that resolved by 5-year cystography in 13/17 (76 %). Of 134 patients with negative 6-month postoperative cystograms, recurrent VUR was found during repeat cystography at 5 years in 4 (3 %). Obstruction developed in 10 (7 %) children, including 3 undergoing Politano-Leadbetter who had the ureter passed through the intestinal wall (Hjalmas et al. 1992).

Reimplantation: Intravesical Versus Extravesical

Extravesical reimplantation creates less gross hematuria and subjective bladder spasm than intravesical repairs.

Bilateral extravesical reimplantation can result in temporary postoperative urinary retention in ≤ 10 % of patients; this is not seen with intravesical techniques.

One RCT randomized 44 children with unilateral VUR grades 2–4 to either extravesical Lich-Gregoir or intravesical Politano-Leadbetter reimplantation (method used to randomize was not stated). Mean age of patients in the two groups was similar (69.7 months [18–110] vs. 62.1 months [8–110]). Extravesical operations were done through an ipsilateral inguinal incision, whereas intravesical procedures used a Pfannenstiel incision. All patients had postoperative catheter drainage for 48 h, urethral for extravesical reimplants, and suprapubic for intravesical repairs. Postoperative pain was assessed using an objective scale, and episodes of bladder spasm quantified. The authors did not state who performed these evaluations, and there is no mention

of blinding. They found that extravesical reimplantation had significantly less bladder spasm and no gross hematuria. Objective pain scale scores were significantly less after extravesical surgery (potentially related in part to the smaller incision), but opioid use was not different. There was no difference in mean postoperative post-void residual urine volumes (time of assessment not stated) (Schwentner et al. 2006).

A prospective study involved 237 patients undergoing extravesical reimplantation, of which 144 were bilateral. Mean age for the entire series was 5.5 years (2 months to 15 years), and all operations were done with a Pfannenstiel incision with postoperative urethral catheter drainage for 12–36 h (reason for varying intervals not stated). Short-term urinary retention developed in 8 % after bilateral reimplantation that did not occur in unilateral cases. This retention resolved within 1 week in all affected patients (Lapointe et al. 1998).

A retrospective review evaluated 220 patients, mean age approximately 5.5 years, who underwent bilateral extravesical reimplantation with postoperative urethral catheterization for 24–48 h from 1991 to 1997. Complete inability to void after catheter removal occurred in 23 (10 %), treated with catheter replacement for another 7–10 days. Retention resolved in 22 during catheterization, while one had clean intermittent catheterization (CIC) for 4 months. Univariate analysis reported grades 4–5 VUR, age ≤ 3 years and male gender, but not treated preoperative voiding dysfunction (not defined) correlated with urinary retention (Barrieras et al. 1999).

Overnight Foley drainage was used in a retrospective series of 50 consecutive toilet-trained children (13 boys), mean age 5 years (2–13 years), undergoing bilateral extravesical reimplantation for VUR grades 1–5. There was no case of postoperative urinary retention (McAhran and Palmer 2005).

Another retrospective study included 41 children with mean age 38 months (16–81) who had bilateral robotic extravesical reimplantation for VUR grades 3–5. All had overnight catheterization followed by post-void bladder scan that found a mean residual of 13 mL. None developed urinary retention (Casale et al. 2008).

Contralateral VUR After Unilateral Reimplantation

Meta-analysis reported approximately 10 % of patients undergoing unilateral reimplantation will have contralateral VUR on postoperative cystography.

One review stated new contralateral VUR ranged from grades 1–5.

Potential risk factors, including one versus more than one and cycled versus non-cycled preoperative cystography, grade of ipsilateral VUR, and history of resolved contralateral VUR, have not been analyzed.

Most this reflux resolves within 1 year of diagnosis.

The first AUA Reflux Guidelines panel reported its review of literature from 1965 to 1994 and indicated that an average of 9 % of unilateral reimplantations demonstrated contralateral VUR postoperatively. Repeat surgery was not recommended for at least 1 year, because most reported new contralateral VUR resolved during that time. Risk factors for contralateral VUR were not reported (Elder et al. 1997).

A retrospective review after either unilateral Cohen or Glenn-Anderson reimplantation found 20 (19 %) of 120 patients had new contralateral VUR. Seventy percent of patients had more than one preoperative VCUG. The authors implied all subjects had only unilateral VUR diagnosed preoperatively. New contralateral VUR was grade 1 in nine, grade 2 in nine, grades 3 and 4 in two each, and grade 5 in one patient. This reflux resolved in 12 (67 %) of 18 with grades 1–2, in 1 with grade 3, and persisted in all with grades 4–5 by 3 years follow-up. Reoperation to reimplant the contralateral ureter was done in 3 (15 %) (Hoenig et al. 1996).

Another retrospective study of 43 unilateral Lich-Gregoir reimplants found new contralateral VUR in 5 (12 %) patients. Of these, four had known prior bilateral VUR with unilateral resolution. The number of preoperative cystograms for the entire group was not stated; nor was the grade of new contralateral reflux. Spontaneous resolution occurred in four of five cases within 1 year (Burno et al. 1998).

Endoscopic Injection: Reflux Resolution

Endoscopic injection is less effective than reimplantation for VUR correction.

Results are best predicted by VUR grade, success diminishing with increasing grade.

Creation of an elevated, coapted mound correlates with VUR resolution, regardless of injection technique (STING vs. intraorifice vs. HIT) or injected volume.

Failures usually are found to have mound loss or shift from under the orifice.

Failure rates of 13–26 % have been reported at repeat cystography more than 12 months after initially successful injection. One report found likelihood for recurrence increased according to initial VUR grade.

Meta-analysis of published results from 63 articles including 5,527 patients and 8,101 ureters reported probability for resolving VUR (defined as negative cystography ≥ 1 month post-injection) with one or more injections using primarily polytetrafluoroethylene, collagen, or Dx/HA was 87 % of patients and 85 % of ureters, with significantly less success in duplicated versus single systems (50 % vs. 73 %).

One injection success probability was as follows:

- 67 % of patients (95 % CI 53.61–78.33)
- 76 % of ureters (95 % CI 70.62–80.10)
- Success by grade: 79 % for grades 1 and 2, 72 % grade 3, 63 % grade 4, 51 % grade 5.

Second injection success probability was as follows:

- 54 % of patients (95 % CI 39.97–68.10)
- 68 % of ureters (95 % CI 61.04–74.29)

Third injection success probability was as follows:

- 34 % of ureters (95 % CI 20.24–50.89) (Elder et al. 2006).

A systematic review of 47 articles and 7,303 ureters regarding Dx/HA injection found similar outcomes, resolution in 77 % of ureters (95 % CI: 76–78 %). The most predictive factor for outcome was VUR grade, with success in 81 % of grade 1 vs. 62 % of grade 5, $p < 0.001$ (Routh et al. 2010).

A prospective study reported a single Dx/HA injection resolved reflux on a 3-month post-injection

cystogram in 70 % of 168 patients and 78 % of 259 ureters having grades 1–5 VUR. Patients failing the initial injection were offered a second, with 61 % of those performed successful, achieving overall reflux resolution in the series in 82 %. The initial 80 children had STING injection technique, whereas the remainder had intraorifice injection—in all cases with the intention to elevate and coapt the orifice. Mean injected volume was 0.54 cc (SD 0.27). Multivariable analysis of factors potentially impacting outcomes (gender, unilateral vs. bilateral VUR, duplicated vs. single system refluxing ureters, VUR grade, injection technique, volume injected, satisfactory versus unsatisfactory post-injection mound morphology) found results independently predicted by the following:

- VUR grade (OR 0.46 [95 % CI .29–72])
- Injected volume < 0.5 cc vs. > 0.5 cc (OR 0.3 [95 % CI 0.09–0.98])
- Desired mound morphology (OR 11.5 [95 % CI 5.3–25])

Increasing VUR grade predicted less success, with a single injection resolving reflux in 100 % grade 1, 83 % grade 2, 73 % grade 3, 53 % grade 4, and 29 % grade 5 ureters. “Satisfactory” mound created in 196 of 243 ureters correlated with 89 % success, while an unsatisfactory mound in 47 ureters resolved reflux in only 36 % (Yucel et al. 2007).

A prospective study compared outcomes in ureters after intraorifice or HIT in consecutive patients treated by a single surgeon. The first 96 ureters had intraorifice injection, while the last 52 had HIT, with single-injection VUR resolution in 86.5 % vs. 79 %, $p = 0.23$. HIT resulted in significantly increased injection volumes versus intraorifice injection (0.68 cc vs. 0.51 cc, $p = 0.002$) (Gupta and Snodgrass 2008).

A retrospective review compared STING to HIT in 301 children and 453 ureters performed by five surgeons. Multivariable analysis found only the surgeon and increasing VUR grade, but not injection technique or volume $< \text{or} > 1$ cc, predicted results (Routh et al. 2007).

A multicenter retrospective analysis reported 87 % of 97 ureters failing Dx/HA injection with a mean 0.86 cc (0.3–2) were found to have mound

volume loss and/or shifting of the implant from under the orifice (Higham-Kessler et al. 2007).

There are limited data regarding recurrent VUR after initial resolution by bulking agents, but available reports indicate success diminishes with time:

- In a report of Dx/HA injection of 334 ureters, 94 % with grades 3–4 VUR, 45 with VUR resolution had subsequent cystography 2–5 years later. Recurrent VUR was noted in six (13 %), four with grade 2 and one each with grades 3 and 4 (Lackgren et al. 2001).
- Another retrospective review of 337 injected ureters reported initial success in 246 (73 %) at 3-month cystography. Of these, 150 (61 %) underwent repeat cystography at 12 months and 39 (26 %) had recurrent VUR, found in 0 % of those originally with grade 1, 19 % of grade 2, 37 % of grade 3, 33 % of grade 4, and 60 % of grade 5 (Lee et al. 2009).

Contralateral VUR After Unilateral Injection

Two studies reported approximately 10 % of children will have new contralateral VUR after unilateral endoscopic injection.

Grade of new VUR ranged from 1 to 4.

Pre-injection VUR grade did not correlate with likelihood for new contralateral VUR.

One study reported a similar average of approximately two pre-injection cystograms in those with and without new VUR.

A retrospective review included 662 children (203 boys) with endoscopic treatment for unilateral VUR using polytetrafluoroethylene or Dx/HA at mean age of 3 years. VUR resolution occurred in all, 83 % with one, 14 % with two, and 3 % with three injections. New contralateral VUR occurred after resolution in 67 (10 %), grade 1 in 16, grade 2 in 17, grade 3 in 27, and grade 4 in 7. There was no correlation between initial VUR grade and likelihood for contralateral VUR. The number of cystograms performed pre- and post-injection in those with versus without new VUR was not stated (Menezes et al. 2007).

Another retrospective report included 126 children (30 boys) with unilateral Dx/HA injection, after excluding those with a history of resolved contralateral VUR. New contralateral VUR was found in 17 patients (13 %) during VCUG 12 weeks post-injection, grade 1 in 9, grade 2 in 6, and grade 3 in 2. There was no difference in mean patient age, mean number of pre-injection VCUGs (1.9 vs. 1.8) or mean VUR grade (2.5 vs. 2.7) in those with and without new contralateral VUR (Elmore et al. 2006).

A third retrospective report analyzed cystoscopic assessment of the contralateral orifice to guide decision-making in unilateral VUR, performing bilateral injection when it had a stadium or worse configuration and/or \geq grade 2 hydrodistention. There were 146 patients with median of 3 (1–6) pre-injection cystograms. Of these, 101 (69 %) were judged to have an abnormal orifice and received bilateral injection versus 45 who were not injected. New contralateral reflux occurred in 8 and 13 %, which was not significantly different (Routh et al. 2008).

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