

Pediatric Vesicoureteral Reflux: Then and Now*

Learning Objective: At the conclusion of this continuing medical education activity, the participant should be able to describe the key considerations and management options for pediatric vesicoureteral reflux.

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INTRODUCTION

The true incidence and clinical significance of vesicoureteral reflux are unknown. Traditionally, obtaining a voiding cystourethrogram has been considered routine in the evaluation of children with a history of either febrile urinary tract infection or prenatal hydronephrosis, as up to 40% and 20% of these patients, respectively, will have urinary reflux.¹⁻⁴ More recently, the practice of aggressive diagnosis and subsequent management of all reflux has been questioned, with a more selective approach increasingly gaining favor.^{5, 6} Once detected, therapeutic options for urinary reflux are diverse, ranging from observation with or without continuous low dose antibiotic prophylaxis to a variety of operative interventions.

While in the majority of cases primary VUR may spontaneously resolve over time, untreated reflux has the potential to contribute to irreversible renal damage as it increases the risk of pyelonephritis. The current consensus is that clinical management should be based on multiple individual factors, including patient age, likelihood of subsequent urinary tract infections, risk of renal parenchymal injury, the projected clinical course and parental preference. Balancing the prevention of potential negative sequelae while limiting the cost and morbidity of treatment is key. In this Update we present current decision making considerations for evaluation and management of pediatric vesicoureteral reflux.

EVOLUTION OF GUIDELINES

AUA guideline on management of primary vesicoureteral reflux in children. The AUA (American Urological Association) published the guideline for the management of primary VUR in children in 1997.⁷ The guideline was updated in 2010 to address the expanding body of literature on diagnosis and treatment of pediatric reflux.⁸ The original guideline provided treatment recommendations, including antibiotic prophylaxis versus surgical repair, based solely on patient age, presence of renal scarring and grade/laterality of persistent reflux. The clinical significance of persistent VUR in the absence of recurrent UTI and upper tract anomalies has been the investigative subject of numerous randomized controlled trials,⁹ perhaps contributing to the inclusion of UTI status and bladder-bowel dysfunction in the more recent AUA guideline.

Given the lack of definitive data, the majority of the updated guideline is based on recommendations and expert opinion as well as several standards. **As VUR may be detrimental to overall health and renal function, initial medical evaluation should include height, weight and blood pressure monitoring, as well as creatinine measurement if bilateral renal parenchymal anomalies are detected.⁸ Screening for and treatment of bladder-bowel dysfunction is of utmost importance, as it influences the risk of febrile UTI, likelihood of spontaneous reflux resolution and success of antireflux procedures.**

To highlight the evolution in the AUA guidelines and following the 1997 guideline, the preferred option for a 5-year-old girl with persistent grade III VUR would be ureteral reimplantation, whereas the 2010 guideline recommendation would be dependent upon UTI and BBD status (fig. 1). Furthermore, if surgery were considered, then endoscopic injection would also be considered. Given the controversy that surrounds the treatment of VUR, not surprisingly the third AUA standard relates to family and patient education about the risk-benefit of management options.

AAP guideline on initial febrile UTI in children 2 to 24 months old. In 2011 the AAP (American Academy of Pediatrics) revised the practice parameters regarding diagnosis and management of initial febrile UTIs in infants and children 2 to 24 months old.⁵ Common presenting symptoms of UTI in children may include fever (>38 °C) and malodorous urine, as well as lower urinary tract symptoms such as dysuria, frequency, urgency and incontinence in older children. The presence of fever and systemic compromise are critical elements. **In order to accurately establish UTI diagnosis, the AAP now requires >50,000 CFU/mL of a uropathogen on catheterized specimen as well as pyuria (≥5 white blood cells) and/or bacteriuria on urinalysis.⁵** Data also now exist to suggest that in the presence of fever and pyuria a colony count as low as 10,000 CFU/mL may be an acceptable threshold for the diagnosis of UTI in infants.^{10, 11} **Importantly, the AAP guideline recommends that children with initial febrile UTI undergo a renal-bladder ultrasound but forego VCUG unless indicated by sonographic findings (ie hydronephrosis, scarring).**

In the RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) trial, a 2-year, multi-institutional, randomized, placebo-controlled study involving over 600 young patients with VUR, antimicrobial prophylaxis substantially reduced the risk of recurrent UTIs by approximately 50%.¹² Likewise, the Swedish Reflux Study demonstrated the benefit of prophylactic antibiotics and endoscopic injection in reducing recurrent pyelonephritis and new renal scarring in a group of 1-year-old children with dilating VUR.¹³

Citing the role of antibiotic prophylaxis in reducing recurrent UTIs in children with VUR and the poor performance of RBUS as a diagnostic tool in the evaluation of febrile UTI, the Section on Urology of the AAP expressed strong opposition to these guidelines with respect to the omission of VCUG in the evaluation of infants with febrile UTI.¹⁴ Despite ongoing debate and new evidence demonstrating the benefit of antimicrobial prophylaxis, the guidelines were reaffirmed by the AAP in 2016, with Roberts et al stating that there is no evidence to suggest that diagnosis of abnormalities missed by more selective imaging is of sufficient clinical benefit to offset the cost, discomfort and radiation of routine VCUG after initial febrile UTI.¹⁰

SCREENING FOR VESICoureTERAL REFLUX

VUR is diagnosed most often after a child suffers a febrile UTI. The method of obtaining a urine specimen is critical for accurate diagnosis. **The AAP requires the presence of >50,000 CFU/mL of a uropathogen as well as pyuria and/or bacteriuria**

ABBREVIATIONS: BBD (bladder-bowel dysfunction), CAP (continuous antibiotic prophylaxis), RBUS (renal-bladder ultrasound), UTI (urinary tract infection), VCUG (voiding cystourethrography), VUR (vesicoureteral reflux)

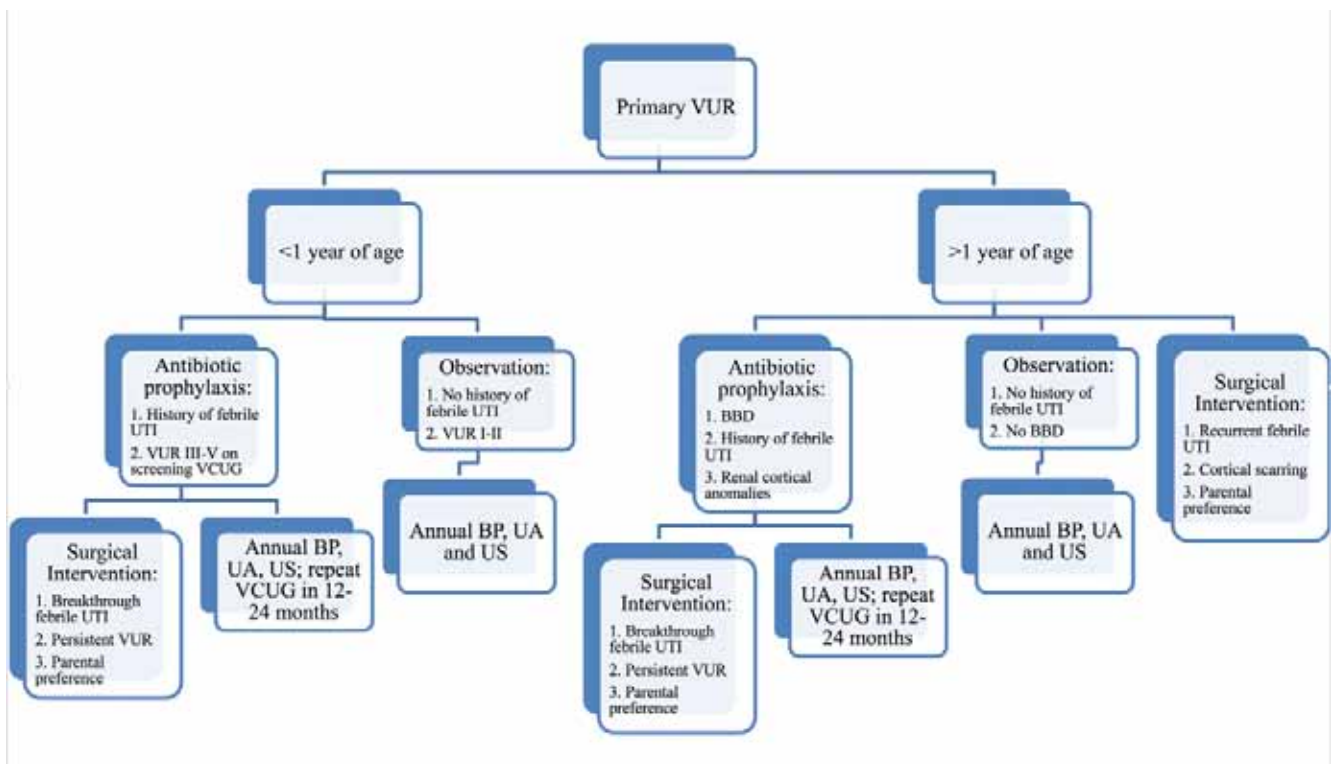


Figure 1. Management algorithm for primary vesicoureteral reflux. It is important to note that circumcision should be offered to all male patients and BBD should be treated in all children, preferably before any surgical intervention. *BP*, blood pressure. *UA*, urinalysis. *US*, ultrasound.

on urinalysis.⁵ Urine specimens should be obtained via catheterization or, less likely, suprapubic aspiration if a clean catch specimen is not feasible, as the diagnosis cannot be reliably established via bagged urine. AAP guidelines recommend that infants/young children with initial febrile UTI undergo RBUS and subsequent VCUG only if the sonogram is abnormal or a second febrile infection develops.⁵ As detailed above, the Section on Urology of the AAP has maintained that VCUG should remain an accepted option after initial febrile UTI.¹⁴ In practice the pros and cons of VCUG should be discussed with parents, and the severity of the UTI symptoms also plays a role in whether to proceed with additional imaging.

While VUR grade is routinely reported after VCUG, other important anatomic and functional findings are often not reported on a regular basis. Given the importance of noting and reporting additional information available from VCUG, as well as its widely varying techniques and quality among hospitals, the American Academy of Pediatrics Sections on Urology and Radiology published a joint standardized protocol in 2016 which should be adhered to when obtaining VCUG for any indication.¹⁵ **ALARA (“as low as reasonably achievable”) and Image Gently principles should be followed, minimizing radiation exposure while still obtaining high quality images.** During cyclic filling (at least 2 voiding cycles are recommended) multiple spot images are obtained and urethral images are obtained during voiding. Scout and post-void images should be obtained, and the maximum volume of contrast instilled as well as the volume at which reflux first occurs should be routinely reported.¹⁵ The volume at which reflux first occurs during bladder filling as a percentage of the predicted bladder capacity is an important predictor of reflux resolution and breakthrough UTIs independent of reflux grade. **Families should be appro-**

priately counseled regarding the risks and benefits of not performing VCUG following an initial febrile UTI including a delay in diagnosing and treating reflux.¹⁶

The role of VUR screening in children with prenatal hydronephrosis is another source of controversy. It remains unproven whether the identification and treatment of children diagnosed with VUR as part of prenatal hydronephrosis evaluation confer any clinical benefit. A prospective study revealed that VUR related to fetal renal pelvis dilation was low grade in 74% of cases, with a 2-year spontaneous resolution rate of >90%.¹⁷ According to these findings, low grade reflux is not necessarily clinically significant.^{17, 18} Conversely, significant renal pelvis dilation (≥ 10 mm), megaureter and/or the presence of cortical abnormalities on RBUS warrant VCUG.^{18, 19} A 2014 multidisciplinary consensus statement suggests that VCUG is an option for all children with prenatal dilation of the urinary tract and is indicated in those with more severe dilation or other abnormalities such as bladder wall thickening.⁴

Sibling screening is no longer routinely performed given the uncertainty of any demonstrable benefit of identifying reflux in the absence of infections or RBUS anomalies. VCUG is recommended in siblings of children with primary VUR if there is a history of UTI or evidence of renal abnormalities on ultrasound.²

TREATMENT OF BLADDER AND BOWEL DYSFUNCTION

Bladder and bowel dysfunction is defined as the combination of functional constipation and lower urinary tract symptoms.²⁰ Despite the generally benign nature of lower urinary tract symptoms, BBD decreases the likelihood of spontaneous VUR resolution, impacts surgical success, and is a significant risk

factor for UTI and renal scarring.²¹⁻²⁴ Infrequent voiding (often compounded by limited fluid intake), especially in the presence of constipation, allows for colonization of the bladder and subsequent development of UTI. Large stool volume in the rectum along with volitional holding due to pain with defecation may hinder complete bladder emptying, contribute to elevated post-void residuals and facilitate bacterial colonization of the bladder.^{25, 26} **Therefore, screening for symptoms indicative of BBD (including urgency, frequency, incontinence, micturition deferral, penile or vaginal pain, constipation, encopresis) should be performed at the time VUR is diagnosed.** There are a variety of validated tools for use in school-aged children which are relatively easy to complete, including the dysfunctional voiding scoring system.²⁷

A “spinning top” urethra may be seen in children with incoordination of the external sphincter and bladder during voiding on VCUG. Additionally, children with overactive bladder might exhibit a “spinning top” urethral appearance due to habitual external sphincter guarding or holding maneuvers during increased bladder pressure or contractions (fig. 2, A).²⁸ The scout film on VCUG can also be used to evaluate stool burden (fig. 2, B). Increased bladder wall thickness and enlarged rectal diameter/stool burden can be visualized on RBUS and correlate with lower urinary tract dysfunction and constipation, respectively.^{29, 30}

The 2010 AUA guideline recommends management of all suspected bladder-bowel dysfunction, preferably before any surgical intervention.⁸ Once BBD has been determined treat-

ment is primarily educational with a focus on optimization of toileting behaviors. **The cornerstone of BBD management in children remains implementation of a bowel program and timed voiding regimen, with additional treatment modalities depending on prevailing symptoms.**^{20, 27, 31} It is important to note that UTI may continue to occur if BBD is untreated, despite medical or surgical management of the VUR. In the CUTIE (Careful Urinary Tract Infection Evaluation) study children with recurrent UTIs could be classified into the 3 risk categories of VUR and BBD (highest risk for recurrent infections), BBD and no VUR, and VUR but no BBD (lowest risk). This underscores the impact of BBD on UTI status and highlights the necessity of effectively managing underlying bladder dysfunction and constipation in children with primary reflux.²²

ANTIBIOTIC PROPHYLAXIS

The use of continuous antibiotic prophylaxis is considered a non-specific approach for prevention of recurrent UTIs. Daily low dose antibiotics is a temporizing measure that allows for spontaneous resolution and/or optimization of bladder and bowel habits while reducing UTI risk. Maintenance of sterile urine in a patient with VUR is believed to negate the risk of renal parenchymal injury and scarring due to pyelonephritis. CAP in children with VUR has been widely used with a reduction in UTIs in those receiving prophylaxis confirmed by the RIVUR trial and Swedish Reflux Study.^{12, 13} In the CUTIE study children with VUR and BBD were at highest risk for recurrent UTI and, therefore, antimicrobial prophylaxis could



Figure 2. Spinning top urethra may be seen on VCUG in patients with incoordination of detrusor and external sphincter during voiding or in those with habitual holding (A). Scout film demonstrates marked stool burden (B).

be of particular benefit in this cohort.²²

While the RIVUR trial revealed a twofold reduction in UTI risk with CAP, there was no significant difference in new renal scars with CAP vs placebo.¹² Continuous antibiotic prophylaxis is considered safe and well-tolerated in general but bacteria with high rates of resistance in patients on CAP have been reported.³² In addition to resistance, early life antibiotic exposure has been associated with increased body mass.³³⁻³⁶ Antibiotics affect the gut microbiota, and the link between altered gut microbiota and human metabolism is becoming increasingly apparent.³⁷ Consequently, the routine use of CAP has been questioned and poor parental compliance with ongoing prophylaxis is well documented. Using a large pharmacy claims database, an adherence rate of just 40% was reported in children with VUR on continuous antibiotic prophylaxis.³⁸

In general, clinicians and parents often opt for intervention based on the likelihood of spontaneous resolution and predicted clinical course, thus placing an emphasis on the ability to predict the chance and timing of spontaneous resolution as well as the likelihood of recurrent febrile infections. Dilating reflux, renal scarring, bladder-bowel dysfunction and VUR at low bladder volumes are all associated with breakthrough infections. Several studies suggest that children on antibiotic prophylaxis without breakthrough infections or evidence of renal injury can be safely observed without prophylaxis or correction of VUR once they reach an age and develop bowel and bladder habits when urinary tract infections are less likely.³⁹⁻⁴² **The AUA guideline recommends CAP for children younger than 1 year with a history of febrile UTI or dilating reflux (ie grades III to V) and those with VUR and BBD, whereas CAP remains an option in other patients.** Bacterial pathogens and antibiotic susceptibility show regional differences, thus successful empirical treatment should be based on local epidemiology and susceptibility rates.^{32,43}

SURGICAL MANAGEMENT

The natural tendency of primary reflux is to resolve over time. Despite a shift toward more conservative management of VUR, some children may still benefit from surgical intervention, particularly those at risk for nephropathy. Therefore, the key focus when selecting patients for surgical correction is to identify those with VUR that is unlikely to resolve and who are at greatest risk for recurrent pyelonephritis along with its sequela of renal injury. Recurrent UTI risk associated with VUR is individualized and depends on several factors, including gender, age, grade, bladder volume at which reflux occurs and the presence of BBD.^{13, 44, 45} **Surgical intervention may be necessary in children with breakthrough febrile UTIs before toilet training, associated urinary tract abnormalities with decreased renal reserve/parenchymal scarring, and febrile UTIs that persist after optimization of bladder and bowel habits.**

Endoscopic injection. Endoscopic correction using an injectable bulking agent as an alternative to open surgery and continuous low dose antibiotic prophylaxis was initially described nearly 4 decades ago. O'Donnell and Puri popularized the concept by performing subureteric injections using Teflon™ paste, ie the “STING” (subureteric Teflon injection) procedure.⁴⁶ Double hydrodistention implantation technique (Double HIT), the hallmark of which is ureteral hydrodistention, allows for direct visualization and injection into the intraluminal ureteral submucosal plane with improved success

rates.⁴⁷ **Proponents of the endoscopic approach highlight benefits including its performance as an outpatient procedure and decreased patient morbidity, while opponents note higher initial failure and recurrence rates compared to ureteral reimplantation.** Endoscopic correction is considered an option in the most updated AUA guideline. Dextranomer hyaluronic acid co-polymer (Dx/HA) is the only injectable agent approved by the U.S. Food and Drug Administration for the treatment of grades II to IV vesicoureteral reflux.

In the Double HIT method the needle is placed into the distended ureteral orifice and inserted in the mid ureteral tunnel at the 6 o'clock position (rather than below the orifice as with the STING technique). Dextranomer hyaluronic acid is injected until a sufficient bulge is produced, which coapts the detrusor tunnel. The second injection at the distal most aspect of the intravesical ureteral tunnel results in coaptation of the ureteral orifice. Hydrodistention is performed following each injection to monitor progress and ensure adequate ureteral coaptation (fig. 3).

Aggregate literature suggests that endoscopic therapy is relatively effective for the treatment of most primary VUR, while stressing the importance of reflux grade and structural/functional bladder anomalies on ultimate success rates. In a systematic meta-analysis of dextranomer hyaluronic acid for pediatric VUR success rates were 89% for grade I, 83% for grade II, 71% for grade III, 59% for grade IV and 62% for grade V reflux.⁴⁸ Due to the lower success rates compared to open ureteral reimplantation, the AUA reflux guideline recommends postoperative VCUG following endoscopic correction of VUR.⁸ Others have suggested that postoperative imaging should be reflective of surgeon experience. RBUS at 6 weeks and 1 year should be considered to screen for acute and chronic asymptomatic ureteral obstruction.

Open ureteral reimplantation. Open reimplantation corrects reflux by increasing the intravesical ureteral length, thus facilitating compression of the ureter against the detrusor muscle, and remains the gold standard surgical technique for VUR. Various open reimplantation techniques have been described including intravesical and extravesical approaches. Cohen cross-trigonal reimplantation (fig. 4) is the most widely used intravesical ureteroneocystostomy technique due to reliable results with 98% success rates and broad applicability.^{8, 49, 50} A catheter is typically left indwelling overnight on the day of surgery. Stenting should be considered when the distal ureter has been tapered, in cases with a thickened or scarred bladder or in reoperative cases in order to minimize the occurrence of temporary postoperative ureteral obstruction. For asymptomatic ureteral obstruction, postoperative ultrasound should be obtained to evaluate the kidneys and ureters for hydronephrosis beyond what would be expected based on the degree of the preoperative VUR. Given the high success rate of ureteral reimplantation at correcting VUR, the need for routine postoperative VCUG is usually dictated by the postoperative clinical course as well as recurrent UTIs.

Robotic assisted laparoscopic ureteral reimplantation. Minimally invasive surgical techniques are increasingly used in the pediatric population for complex reconstruction, and robotic technology has bridged the gap between open and laparoscopic surgery with magnified 3-dimensionality and superior stereoscopic visualization. While open surgery remains the gold standard for the correction of vesicoureteral reflux, robotic reim-

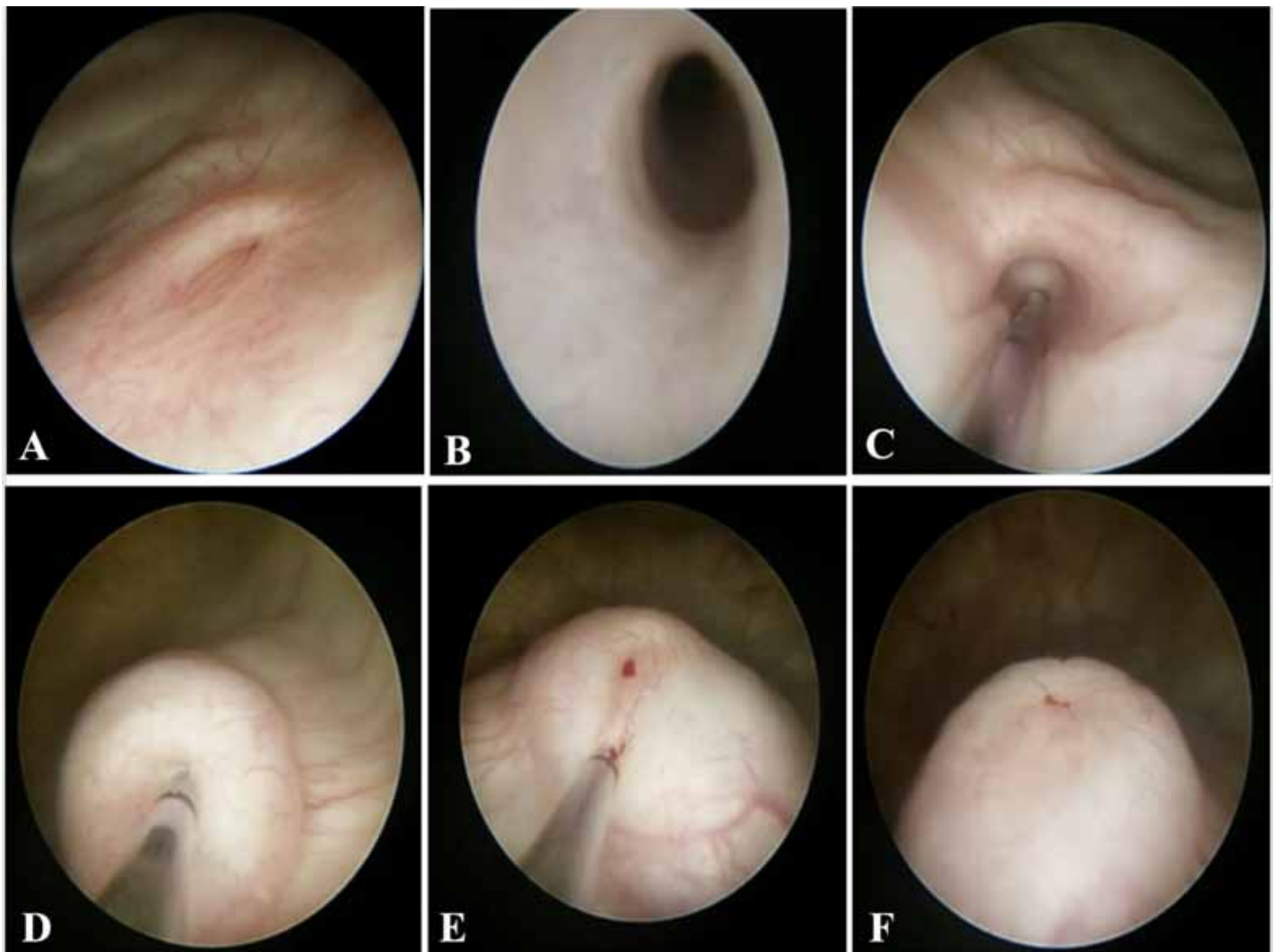


Figure 3. Double HIT method. Bladder is drained and ureteral orifice is visualized (A), followed by hydrodistention with visualization of extramural ureter (B). Proximal HIT is then performed with needle inserted into mid ureteral tunnel at 6 o'clock position (C). Sufficient bulking agent is injected to produce bulge which coapts tunnel (D). Distal HIT is subsequently performed (E), leading to coaptation of ureteral orifice (F).

plantation has gained increasing acceptance.^{51,52}

Robotic reimplantation is typically performed in an extravesical fashion. The camera port is placed in the umbilicus, and the procedure can be readily performed using 2, 8 mm robotic ports without the routine use of an accessory port (fig. 5). Similar to open ureteroneocystostomy, a catheter is typically left indwelling for 24 hours and the need for stent(s) is based on anatomy and surgeon preference.

VUR resolution rates after extravesical robotic ureteral reimplantation reported in the literature range from 66.7% to 100% in multiple relatively small series, with an overall 91% success rate upon pooling these series.⁵³ A multi-institutional retrospective study revealed a radiographic success rate of 87.9% and, more recently, a large prospective multi-institutional group reported a slightly higher resolution rate of 93.8%.^{54,55} Compared to open surgery, robotic surgery has been associated with decreased morbidity, less postoperative pain, lower analgesic requirements, quicker postoperative recovery and shorter hospital stays. However, there are multiple reports of higher

complication rates with the robotic than the open approach.^{56,57} **As with other robot-assisted laparoscopic operations, advantages compared to an open approach seem most apparent in older children, and must be balanced against operative time and cost considerations.** Long-term studies demonstrating comparable efficacy, cost, complications and improved quality of life benefits of robotic surgery over standard open repairs are needed.

FOLLOW-UP

Children with VUR should undergo annual blood pressure monitoring, and height and weight assessment through adolescence, as well as urinalysis for proteinuria/bacteriuria with culture if infection is suspected. These same general measures are also recommended for patients with spontaneous or surgical resolution of VUR if there is a history of abnormality on ultrasound. Renal ultrasound has been recommended annually to monitor renal growth, and VCUG can be obtained every 1 to 2 years depending on the clinical course of patients with

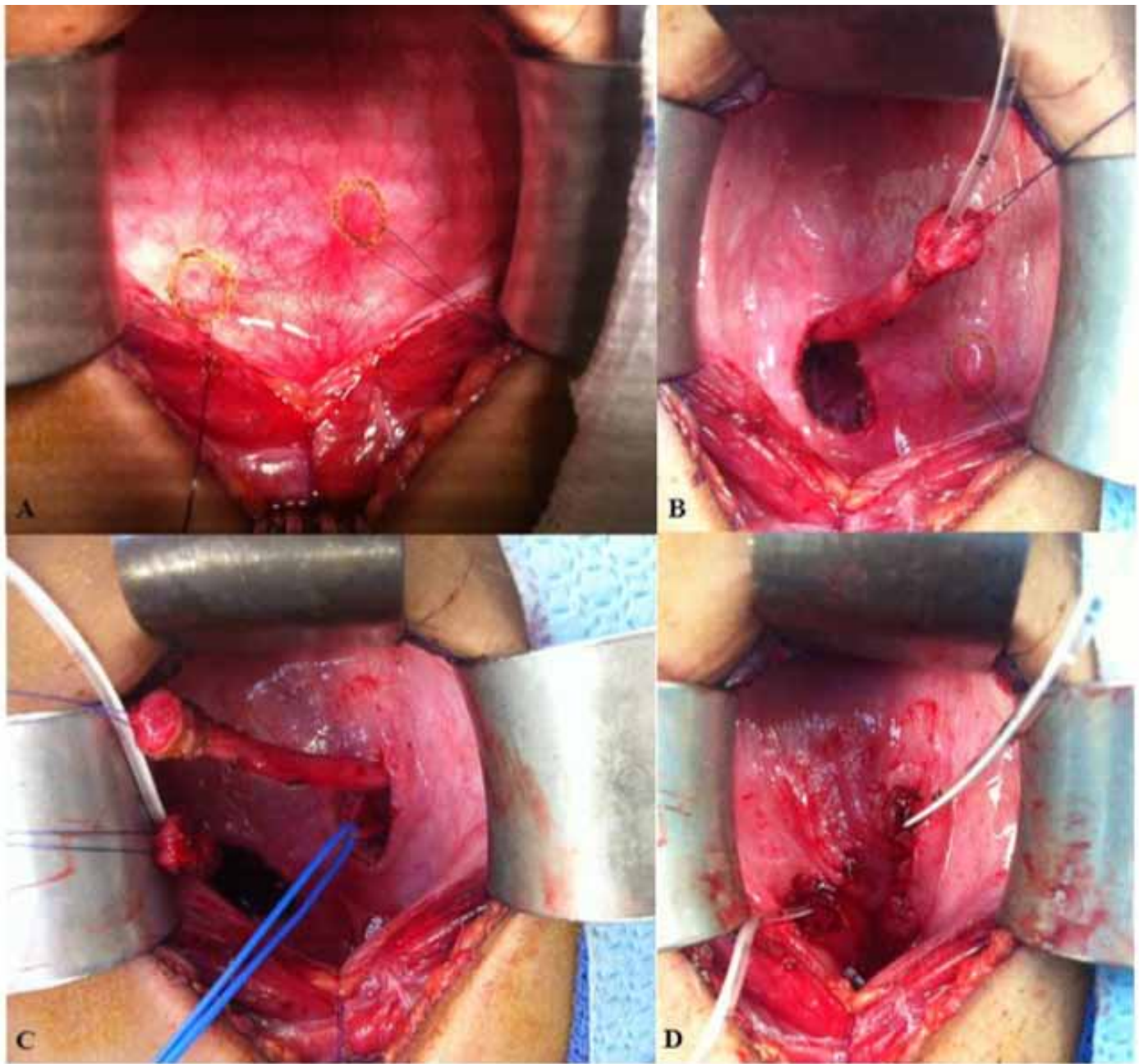


Figure 4. Bilateral Cohen cross-trigonal reimplant. Ureteral orifices are tagged and needlepoint cautery is used to circumscribe orifices (A). Ureter is mobilized to ensure tunnel length is 5 times ureteral diameter (B). In boys it is important to ensure preservation of vas deferens (encircled with blue vessel loop) (C). After creation of tunnels, ureters are approximated to neo-orifices bilaterally, and feeding tubes are temporarily passed to ensure there is no obstruction (D).

persistent reflux.⁸ **Follow-up RBUS should be done in patients undergoing surgical intervention to assess for silent ureteral obstruction, and VCUG is recommended for those treated endoscopically.** Furthermore, while the incidence of significant comorbidities in children with VUR is often minimal at diagnosis, long-term concerns with respect to disease specific morbidity, such as hypertension or end stage renal disease, warrant discussion with the parents or guardians.

CONCLUSIONS

Controversy persists regarding the optimal management of primary vesicoureteral reflux in the pediatric population. Antibiotic prophylaxis is most often considered in infants and children with recurrent febrile infections. Bladder and bowel dysfunction should be screened for and addressed before any surgical intervention. Management of VUR should be individualized, and focused on the goals of preventing recurrent UTI and renal injury as well as minimizing treatment and follow-up morbidity.

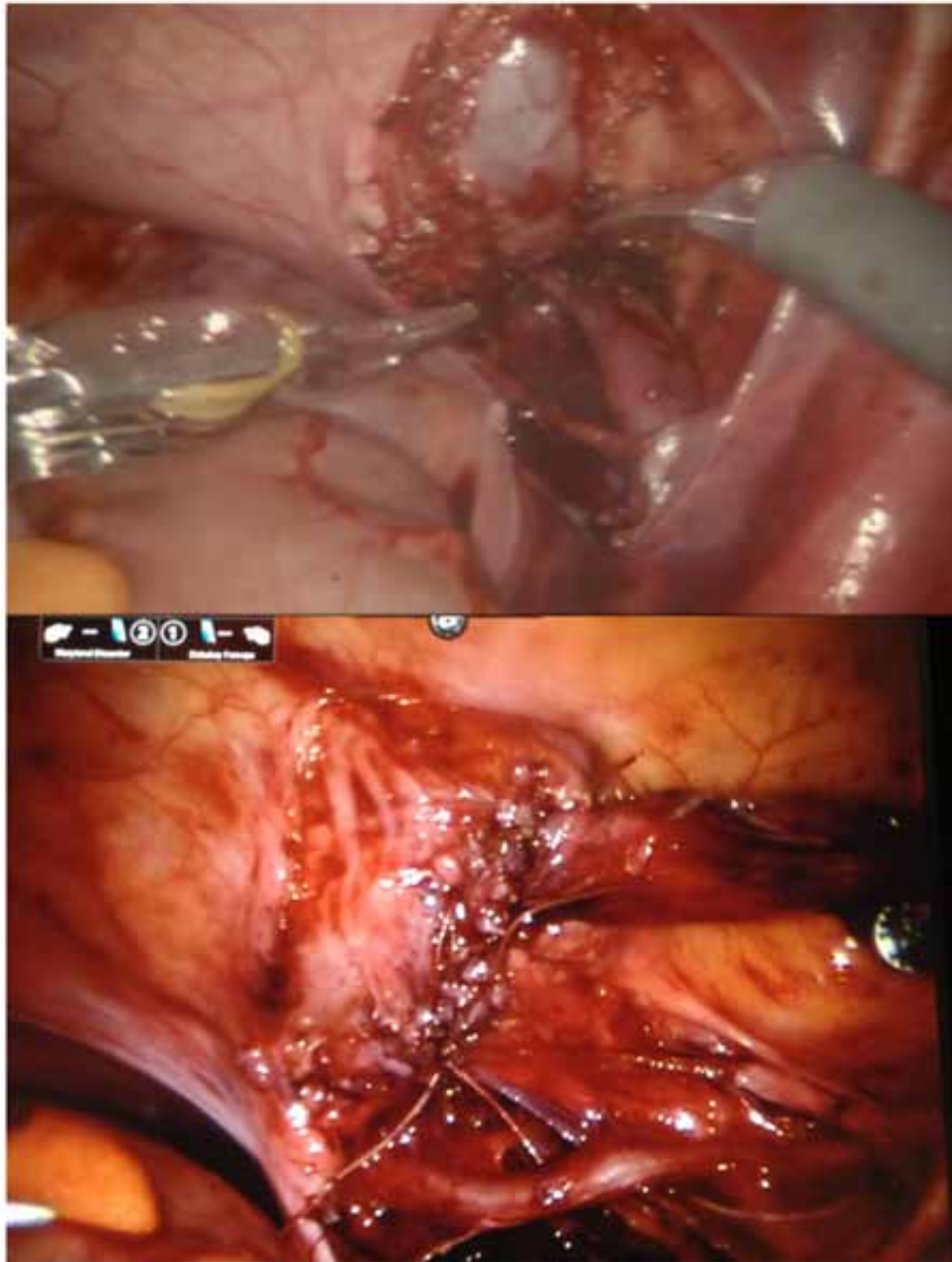


Figure 5. Robotic extravesical ureteral reimplantation. Refluxing ureter is identified and followed distally to bladder hiatus. Juxtavesical ureter is dissected and detrusor trough is created by incising serosa and detrusor down to mucosa using combination of electrocautery and sharp dissection, extending laterally from ureteral hiatus. Refluxing ureter is then advanced caudally below detrusor muscle and detrusor is then approximated over ureter using running suture.

DID YOU KNOW?

- Children with VUR should undergo initial medical evaluation, including height, weight and blood pressure assessment, as well as creatinine measurement if bilateral renal parenchymal anomalies are detected.
- The AAP diagnosis of a UTI requires $>50,000$ CFU/mL of a uropathogen as well as pyuria and/or bacteriuria on urinalysis from a properly obtained sample.
- Screening for and treatment of bladder-bowel dysfunction is of utmost importance as it influences the risk of febrile UTI, likelihood of spontaneous reflux resolution and success of antireflux procedures. Therefore, screening for symptoms indicative of BBD (including urgency, frequency, incontinence, micturition deferral, penile or vaginal pain, constipation, encopresis) should be performed at the time of VUR diagnosis.
- Follow-up renal and bladder ultrasound to assess for silent ureteral obstruction should be performed in patients treated surgically and VCUG is recommended for those treated endoscopically.

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Study Questions Volume 39 Lesson 9

1. The diagnosis of *Escherichia coli* UTI in a 10-month-old afebrile girl is best made with a
 - a. bag specimen urine with positive leukocyte esterase, positive nitrites and >100,000 CFU
 - b. catheterized urine with positive leukocyte esterase, negative nitrites and >10,000 CFU
 - c. catheterized urine with positive leukocyte esterase, negative nitrites and >50,000 CFU
 - d. catheterized urine with negative leukocyte esterase, negative nitrites and >100,000 CFU
2. A 4-year-old girl with a history of 2 febrile UTIs is found to have unilateral grade IV vesicoureteral reflux. According to the AUA guidelines the next step is
 - a. screening and treatment of constipation
 - b. serum creatinine measurement
 - c. functional renal cortical imaging
 - d. prophylactic antibiotics
3. According to the American Academy of Pediatrics joint urology and radiology statement, standardized VCUg should include
 - a. a single voiding phase
 - b. proximal urethral diameter
 - c. bladder volume when reflux first occurs
 - d. estimate of fecal distention/rectal diameter
4. Administration of prophylactic antibiotics to children with VUR has been associated with a subsequent decrease in
 - a. UTIs
 - b. bacterial resistance
 - c. bladder dysfunction
 - d. renal scars
5. Compared to open ureteral reimplantation, endoscopic subureteric injection for the treatment of VUR is associated with
 - a. increased morbidity
 - b. decreased success rate
 - c. decreased long-term recurrence
 - d. increased bladder dysfunction

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