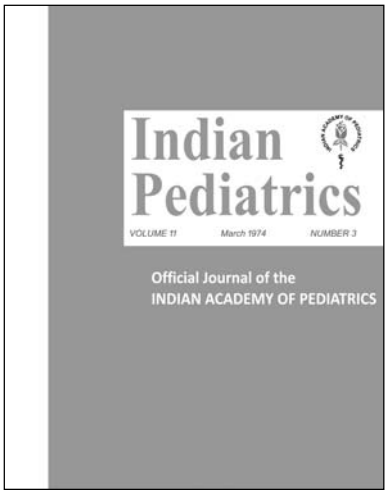
Evolution in Management of Vesicoureteral Reflux in Children

Amar Jeet Mehta,[1] Maneesha Bhargava,[2] Ruchi Rao[1]

[1]Department of Pediatric Nephrology, Rajasthan University of Health Sciences (RUHS) College of Medical Sciences, Jaipur, Rajasthan, India
[2]Department of Pediatric Nephrology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India

Vesicoureteral reflux (VUR) is an anatomic and/or functional disorder resulting in the retrograde flow of urine from the bladder in to the ureter with potentially serious consequences in later life [1]. Galen for the first time described the anatomy of VUR and Da Vinci postulated an antireflux mechanism to prevent urine from returning into the upper tracts [2]. Hodson and Edwards discovered the association of VUR with renal scarring due to recurrent bacterial infection [3]. Since then, several research works have demonstrated an exponential relationship between the grade of reflux and the number of urinary tract infections (UTIs) and renal scarring. Working within this concept, there was concern that uncontrolled reflux would eventually lead to reflux nephropathy and end-stage renal disease (ESRD).



Vesicoureteral reflux (VUR) affects about 1% of all children. Among infants prenatally identified to have hydronephrosis by ultrasonography (USG) and who were later screened for VUR, the prevalence of VUR was reported as 16.2% (range 7-35%) [4]. In a recent study, siblings of children with VUR had a 27.4% (range 3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a still higher incidence of about 35.7% (range: 21.2-61.4%) [5].

PAST

Before 1970s studies on VUR in India were very few. In 1974, Taneja et al published a retrospective study on children manifesting VUR [6]. In their study, the incidence of VUR was reported as 29.1% with a male preponderance (male to female ratio 9.4:1). The diagnostic modalities used to determine the cause and the degree of reflux were plain skiagram, excretory pyelography, voiding cystourethrography (VCUG) and cystourethroscopy. More than 50% of patients underwent surgical procedures whereas others were treated conservatively. Mortality was 11.2%. Similar studies in that era included diagnostic modalities like radiographic studies including plain skiagram, excretory pyelogram, voiding cystourethrogram, cystourethroscopy under general anesthesia and visual demonstration of reflux by instillation of indigo carmine into bladder by the cystoscopy [7].

In 1952, Hutch performed the first antireflux surgery which led to the investigation of relationship between VUR and upper urinary tract damage [8]. In 1958, Politano and Leadbetter introduced intravesical ureteral reimplantation, a new surgical corrective procedure for VUR [9] as an advancement over the prior surgical therapies which aimed to reduce resistance at the bladder neck. Ureteral reimplantation negated the concept that bladder outlet resistance was the major cause of reflux [10]. In 1977 Edwards et al reported high rates of spontaneous resolution of reflux (71%) on low dose continuous antibiotic prophylaxis (CAP) [11].

The routine use of prenatal imaging was brought in 1980s which made it easy to diagnose VUR early in those, who had prenatal dilatation on sonography. Prior to this, VUR was primarily identified after the onset of a febrile urinary tract infection (FUTI) episode. 1980s was also significant for the introduction of a standardized grading system by the International Reflux Study Committee [12]. VCUG became helpful for demonstration of reflux on imaging studies. The International Reflux Study proposed

Correspondence to: Dr Amar Jeet Mehta,
Pro-Vice Chancellor,
Rajasthan University of Health Sciences (RUHS) College of Medical Sciences, Jaipur, Rajasthan 302033, India.
dramarjeetmehta@yahoo.com

five grades of reflux based on the VCUG and discussions of management became more specific. In an attempt to bring out minimal invasive surgery in 1980s endoscopic injections for the treatment of VUR was introduced; however, the procedure gained popularity in 2001 when FDA approved dextranomer/hyaluronic acid (Deflux) [14]. Although it was initially a popular procedure, the use gradually decreased in USA because of certain discrepancies.

PRESENT

Micturating cystourethrogram (MCU) is the gold standard to diagnose and stage VUR, which is present in approximately one-third of children with UTI. This implies that if imaging for VUR is performed in all children with UTI, two-thirds will undergo the inconvenience and hazards of imaging with negative results. Hence, the MCU study should be reserved for children with high suspicion of VUR. VUR is conventionally graded on MCU using the International Reflux Study classification [11]. Other modalities are Contrast enhanced Ultrasonography (CE-USG), direct radionuclide cystography (DRCG), indirect radionuclide cystography (IRCG), and magnetic resonance urography (MRU). Radionuclide studies such as DMSA (dimercaptosuccinic acid) scan and video urodynamic studies are important only in patients in whom secondary reflux is suspected.

Cystoscopy has a limited role in evaluating reflux except in patients with infravesical obstruction or ureteral anomalies that might influence therapy. In most patients, even high grades of VUR resolves spontaneously over a period of time. Hence, the primary focus during management of patients with primary VUR is to prevent recurrence of UTI.

There are mainly two treatment approaches for patients with VUR: conservative (nonsurgical) and surgical as per recent ISPN guidelines [16]. In most patients, even high grades of VUR resolve spontaneously over a period of time. Hence, the primary focus during the management of patients with primary VUR is to prevent recurrence of UTI. Surgical reimplantation be considered in patients with high-grade VUR with recurrent breakthrough febrile UTI on antibiotic prophylaxis.

The conservative approach includes watchful waiting, intermittent antibiotic prophylaxis or continuous antibiotic prophylaxis (CAP), and bladder rehabilitation in patients with lower urinary tract dysfunction [12]. Most frequently used agents for CAP are single low doses (one-third of the treatment dose) of amoxicillin and trimethoprim (patients aged < 2 mo) or trimethoprim sulfamethoxazole or nitrofurantoin (for older infants). Many clinical trials on use of CAP in VUR are available with mixed results.

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation. Several bulking agents have been used over the past two decades. They include polytetrafluoroethylene (PTFE, or Teflon), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, and more recently, a solution of dextranomer/hyaluronic acid (Deflux). The best results have been obtained with PTFE [15], but PTFE has not been approved for use in children because of concerns about particle migration [17]. Open surgical techniques share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. The most popular and reliable open procedure is the Cohen cross-trigonal reimplantation. Transperitoneal laparoscopic approaches both conventional and robot assisted include extravesical and pneumovesicoscopic intravesical ureteral reimplantation. Recent ISPN guidelines suggest open ureteric reimplantation over endoscopic correction as it has a higher success rate of resolution of VUR and a lower complication rate [16-19]. It is the preferred modality for those with Bowel Bladder Dysfunction (BBD) [20] and following failure of endoscopic correction [21]. However, it is associated with prolonged hospital stay, greater need for postoperative analgesia, and the increased risk of postoperative complications. While open reimplantation (extra- or intra-vesical approach) is the gold standard, laparoscopic or robotic-assisted laparoscopic reimplantation has a lower average length of hospital stay [22]. The disadvantages include a longer learning curve, longer operating time, and higher cost. These techniques can be considered only as alternate options based on the availability of surgical expertise and parental preference.

FUTURE

Management of VUR continues to be a dynamic subject and varies in practice patterns between early intervention *vs* observation only. It is still a potential field with future research to further stratify VUR patients into those who are at high risk for renal damage versus those with low risk, to individualize and better management. Preventing future UTIs, renal scarring, reflux nephropathy and hypertension should be goals of managing VUR. The topdown approach with upper tract imaging (USG and radionuclide scan) and selective vesicocystourethrogram (VCUG) is a new noninvasive approach in the evaluation of children after their first FUTI. Contrast enhanced-USG may be the future imaging technique with the advantage of being free of radiation risk. Identification of the underlying genetic defects for VUR will help identifying patients with

sporadic VUR, more so in familial VUR. In addition, those at risk of developing renal failure may benefit from an analysis of genotype-phenotype correlations. Such studies would also find the association of certain mutations with reflux grade. Finally, a VUR gene may allow a biochemical understanding of VUR, and possibly add to the development of new approaches to treatment [23]. New modalities like the use of procalcitonin and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels and other biomarkers can be considered as parameters in further studies for development of a universal tool [24].

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Fanos V, Cataldi L. Antibiotics or surgery for vesicoureteric reflux in children. Lancet. 2004;364:1720-2.
2. Schultheiss D, Grünewald V, Jonas U. Urodynamics in the anatomical work of Leonardo da Vinci (1452–1519). World J Urol. 1999;17:137-43.
3. Hodson CJ, Edwards D. Chronic pyelonephritis and vesicoureteric reflex. Clin Radiol. 1960.11:219-31.
4. Sargent MA. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol. 2000.30:587-93.
5. Skoog SJ, Peters CA, Arant Jr BS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/Infants With Prenatal Hydronephrosis. J Urol. 2010; 184:1145–51.
6. Taneja et al. Vesico-ureteral reflux in children. Indian Pediatr.1974;11:189-97
7. Amar AD Demonstartion of vesicouretral reflux without radiation exposure. J Urol. 1964;92:286-8.
8. Hutch JA. Vesico-ureteral reflux in the paraplegic: cause and correction. J Urol. 1952;68:457–69.
9. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. 1958. J Urol. 2002;167:1415-21; discussion 1422.
10. O'Donnell B, Moloney MA, Lynch V. Vesico-ureteric reflux in infants and children: results of supervision, chemotherapy and surgery. Br JUrol 1969;41:6-13.
11. Edwards D, Normand IC, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. Br Med J. 1977;2:285-8.
12. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol. 1985;15:105-9.
13. Dias CS, Silva JM, Diniz JS, et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J. 2010;29:139-44.
14. Lendvay TS, Sorensen M, Cowan C, Joyner B, Mitchell M, Grady R. The evolution of vesicoureteral reflux management in the era of dextranomer/hyaluronic acid copolymer: a pediatric health information system database study. J Urol 2006;176:1864-7.
15. Puri P, Granata C. Multicenter survey of endoscopic treatment of vesicoureteral reflux using polytetrafluoroethylene. J Urol. 1998;160:1007–11, discussion 103
16. Hari P, Meena J, Kumar M, et al; Indian Society of Pediatric Nephrology. Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux. Pediatr Nephrol. 2023 Oct 28. Epub ahead of print.
17. Steyaert H, Sattonnet C, Bloch C, Jaubert F, Galle P, Valla JS. Migration of PTFE paste particles to the kidney after treatment for vesico-ureteric reflux. BJU Int. 2000;85:168-9.
18. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics. 2010;125:1010-9.
19. Holmdahl G, Brandström P, Läckgren G, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol. 2010;184:280-5.
20. Miyakita H, Hayashi Y, Mitsui T, et al. Guidelines for the medical management of pediatric vesicoureteral reflux. Int J Urol. 2020;27:480-90.
21. Bastos JM Netto, Rondon AV, Machado MG, et al. Brazilian consensus on vesicoureteral reflux-recommendations for clinical practice. Int Braz J Urol. 2020;46:523-37.
22. Deng T, Liu B, Luo L, Duan X, et al. Robot-assisted laparoscopic versus open ureteral reimplantation for pediatric vesicoureteral reflux: a systematic review and meta-analysis. World J Urol. 2018;36:819-28.
23. Eccles MR, Bailey RR, Abbott GD, Sullivan MJ. Unravelling the genetics of vesicoureteric reflux: a common familial disorder. Hum Mol Genet. 1996;5:1425-9.
24. Shaikh N, Borrell JL, Evron J, Leeflang MM. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. Cochrane Database Syst Rev. 2015;1:CD009185.