REVIEW ARTICLE

# Emerging Landscape of Antibiotic Resistance and Use of Endoscopic Injection in Vesicoureteral Reflux

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## Abstract

Vesicoureteral reflux (VUR) in children is often treated with antimicrobials for prolonged durations, which often leads to antimicrobial resistance. In this context, this review article discusses the use of endoscopic injection in VUR as a safe and efficacious option for these children.

The literature pertaining to VUR- its clinical manifestation and management, antibiotic resistance- with special reference to management of VUR, and endoscopic dextranomer/hyaluronic acid gel injection for management of VUR was reviewed by identifying key words in a PubMed search.

Vesicoureteral reflux is managed using antibiotic prophylaxis, urotherapy, or surgical correction (open, endoscopic injection therapy, or laparoscopic). Continuous antibiotic prophylaxis for urinary tract infections in VUR can lead to antibiotic resistance. Urotherapy cures about 75% of cases with dysfunctional voiding and the rest have to be managed at specialized centers. While open surgery provides relief of VUR and related complications in majority, it requires hospitalization. Endoscopic injection of dextranomer/hyaluronic acid gel into the submucosa of bladder or ureter near ureteral orifice increases the tissue bulk and creates a valve function. Various studies show the efficacy and safety of endoscopic injection of dextranomer/hyaluronic acid gel in VUR. The use of endoscopic injection being a non-invasive modality, can be performed in children with VUR in the outpatient department, precluding hospitalization.

In view of the threat of developing antimicrobial resistance and also realising the need for definitive treatment of VUR, endoscopic injection is an efficacious and safe option in primary VUR.


## Introduction

Antimicrobial therapy has become one of the pillars of modern medicine over the last 60 years. The fear of death due to microbial infection is now almost obsolete in the developed world due to availability of various antimicrobial agents, but on the other side, this is threatened by the development of resistance to antimicrobials. The arrival of these antimicrobial agents marked the beginning of an era of optimism and enthusiasm regarding conquest over infectious diseases. This optimism started fading with the development of resistance to these agents in bacteria.[1] This is particularly a major problem in developing countries where the burden of infections is very high and cost constrains the replacement of older antimicrobial agents. The infectious disease burden in India is one of the highest in the world; therefore, antimicrobial agents have a role to play in limiting morbidity and mortality in India.[2]

Primarily, drug resistance has been recognized as a medical problem. When antimicrobial agents are used either in human beings or animals, there is always a risk of the development and spread of antibiotic resistance in bacteria. Therefore, there is need of each country to adopt strategies fit to its own condition.[2]

### Antimicrobial Resistance – A Global Threat

Antimicrobial resistance is a major problem that strikes at the centre of infectious disease control. Antimicrobial resistance and its global spread threaten the continued effectiveness of antimicrobials and also risks global health security.

Infections caused by multidrug-resistant (MDR) bacteria are often associated with prolonged and expensive hospitalization. The most important factor behind the evolution of drug resistance in bacteria is the drug selection pressure, which involves use of drugs in both human and animals.

In many cases, these infections lead to higher morbidity and mortality. Multi-drug resistant organisms have been an epidemiological concern as they may spread locally, regionally or globally through individual contacts, poor sanitation, travel or food chain.[3]

For antimicrobial resistance to become a clinical problem, three events must occur.

1. First, an individual pathogenic bacterium must acquire resistance to the antimicrobial agent in question. This could occur by a spontaneous mutation in one of its genes, which might make a target protein less susceptible to the antibiotic by modification of the antibiotic binding site. Alternatively, the bacterium could gain a gene encoding antimicrobial resistance via horizontal transfer of deoxyribonucleic acid from a different bacterial strain.
2. Second, the newly resistant bacterium must multiply in such a fashion that its resistance-encoding gene spreads in the local bacterial

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population and cannot be wiped out through fluctuations in the number of organisms carrying this gene.

3. Third, the resistant bacterial strain must spread beyond the local bacterial population where it originated, until it infects a significant number of humans and becomes clinically significant.[4]

Currently although antimicrobial resistance is a grave threat in many places in India, the problem remains largely unrecognized mainly because there are not much studies published and also because the surveillance system in India does not match up the magnitude of the problem . The threat of antimicrobial resistance came into light in a big way only when the New Delhi metallo-β-lactamase-1 (NDM1) was first reported in 2009. New Delhi metallo-β-lactamase-1 is an enzyme produced by the gene blaNDM1, carried on plasmids which could be transferred to many bacterial species, for example *Klebsiella pneumoniae* and *Escherichia coli*, thereby conferring resistance to multiple antibiotics, including carbapenems.[2]

The first epidemic reported to be caused by an antibiotic-resistant bacterial strain was by chloramphenicol resistant *Salmonella typhi* in 1972 in Mexico.[5] Subsequent outbreak was reported by the chloramphenicol-resistant *S. typhi* strains in Kerala, India. Since then, MDR *S. typhi* strains showing resistance to chloramphenicol, ampicillin, and trimethoprim have been reported in the Indian subcontinent, Southeast Asia, and Africa.[6]

New Delhi metallo-β-lactamase-1, a metallo-beta-lactamase (MBL), belonging to the family of carbapenemases, was first identified in isolates of *K. pneumoniae* and *E. coli*, both recovered from a patient in Sweden after his treatment in a hospital in New Delhi, India.[2] Thereafter, studies reported NDM1 from a tertiary centre in Mumbai, following isolation of MDR *Enterobacteriacae* in other cities.

Thereafter, resistance to a further wide range of antibiotics has been reported among hospital-acquired gram-negative organisms (*Acinetobactor, Pseudomonas, Klebsiella, E. coli, Salmonella, Neisseria gonorrhoeae*). The prevalence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* is increasing worldwide and infections with ESBL producing *E. coli* are posing major threat in many countries including India.[7]

Immediate strategies to combat such emerging landscape of antibiotic resistance should include rational use of antimicrobial agents, public health education, behavioural change and communication strategies.

Several disease conditions characterised by infections are treated with the use of antibiotics. However, injudicious use of antibiotics in these disease conditions leads to development of antibiotic resistance in these patients. One such condition is vesicoureteral reflux (VUR) in which patients suffer from urinary tract infections (UTIs).

## Vesicoureteral Reflux and its Clinical Manifestations

Vesicoureteral reflux is characterized by the retrograde flow of urine from the bladder to the upper urinary tract.

The prevalence of VUR is estimated to be around 0.4% to 1.8%. The prevalence of VUR is higher in siblings of patients with VUR (46%), children with recurrent UTI (30%), infants with prenatal hydronephrosis (16%), and the presence of congenital anomalies of the urinary tract such as posterior urethral valves (60%), cloaca (60%), and duplex kidney (46%).[8]

Children, who present with hydronephrosis in intrauterine life, identified prenatally via ultrasonography; often present with clinical UTI in early years of life.[9]

The diagnosis of UTI in children can be difficult. Children often present with nonspecific clinical features. Pyelonephritis in young children usually manifest with abdominal discomfort rather than with the classic flank pain and tenderness observed in adults.[10]

Globally, VUR is considered a crucial etiological factor for post-UTI renal scarring in children. Vesicoureteral reflux predisposes children to UTI and pyelonephritis, and both are associated with significant renal scarring.[11]

## Management of VUR

The goals of management of VUR include the prevention of reflux and prevention of pyelonephritis, reflux nephropathy, and other complications of reflux. The various treatment strategies include antibiotic prophylaxis, urotherapy (correction of voiding dysfunction), and surgical correction (open, endoscopic injection therapy, or laparoscopic).[12]

### *Antibiotic prophylaxis*

The knowledge of the relationship between renal scarring, UTI, and VUR paved the path for the emergence of the clinical use of prophylactic antibiotics in the early 1970s. This was largely due to the work of Normand and Smellie, who had shown a decrease in the incidence of UTI in children with VUR on Continuous Antibiotic Prophylaxis (CAP). As a clinical strategy, CAP became the recommendation of the American Urological Association guideline in 1997.[13]

However, the patients suffering from primary VUR generally belong to the paediatric age group and injudicious and long-term usage of antibiotics for prevention and/or treatment of these UTIs often is associated with the risk of onset of antibiotic resistance in these patients.

Concern is growing among medical practitioners about the long-term use of CAP in VUR patients. Poor compliance to antibiotic regime is also common. These facts against long-term antibiotic use have led to a rethinking about the use of CAP in these children.

### *Urotherapy or bladder training*

It is a non-surgical, non-pharmacological treatment of lower urinary tract symptoms of neurogenic and non-neurogenic bladders. It mainly includes - pelvic floor training and biofeedback. Urotherapy cures about 75% of children with overactive bladder and dysfunctional voiding. Non-responders should be referred to specialized centres for further urodynamic investigations.[14]

### *Surgery*

Decisions for surgery are based on numerous factors like patient's age, health, grade of reflux, clinical course of the disease, compliance to antibiotics, presence of renal scarring, and parental preference. Prevention of febrile UTI or pyelonephritis is one of the major goals of surgical management. Surgical treatment of VUR reduces the occurrence of pyelonephritis. Patients with recurrent UTI and/or persistent reflux benefit most from surgery.

Open surgery prevents reflux by

increasing the length of the intravesical ureter and thereby facilitating compression of the ureter against the detrusor muscle during the urinary bladder filling. In endoscopic repair, the dextranomer/hyaluronic acid gel is injected into the submucosa of either the bladder or the ureter near the ureteral orifice. As a result, the ureteral orifice closes because of the increase in tissue bulk, creating a valve function. This allows coaptation of the ureter during filling and contraction of the bladder, making it more difficult for urine to reflux, or flow, back into the ureter.

Open surgery generally requires hospitalization for management of post-operative pain as well as for temporary urinary catheter drainage whereas the endoscopic repair is an outpatient procedure (some surgeons even prefer the minor operation theatre) with minimal post-operative pain and no need for urinary catheter.[15]

### Antibiotic Prophylaxis in Vesicoureteral Reflux and Development of Antibiotic Resistance

There has been strong evidence for overuse of antibiotics in children suffering from paediatric urological disorders. Febrile UTI is one of the most serious bacterial infections in the paediatric age group because of the involved risk of renal scarring with permanent damage to the kidneys in about 5%.[16]

As reinfection in these children is very common, physicians prescribe daily low-dose antibiotic prophylaxis to prevent further UTIs in these children especially those with VUR and prenatal hydronephrosis.[17]

In 2010, a Cochrane Review studied the efficacy and safety of long-term chemoprophylaxis to prevent recurrent UTIs in the paediatric age group. The Cochrane Review concluded that even though long-term chemoprophylaxis reduces the risk of recurrent UTIs in children, there is a simultaneous highly increased risk of microbial resistance.[18]

The choice of antibiotic for chemoprophylaxis is also very crucial. Cheng (2008) found that children receiving cephalosporins for prophylaxis tend to develop ESBL-producing bacteria or MDR bacteria for breakthrough UTIs; therefore, it was suggested that these antibiotics are not suitable for prophylactic use in patients with VUR.[19]

Also compliance with chemoprophylaxis is often poor, particularly in the lower socioeconomic strata and poor compliance leads to increased risk for antibiotic resistance. Younger age, recurrent hospitalizations, and visits to the physicians have been observed to be associated with improved compliance, suggesting that probably compliance to chemoprophylaxis may be improved through increased patient contact with the healthcare system.

Appropriate prescribing of antibiotics is necessary to improve patient outcomes and to help prevent the emergence of antibiotic resistance. Although there has been a reduction in use of antibiotics in the United States by 17% in the last few years, there is still evidence of antibiotic overuse and misuse (The Center for Disease Dynamics, Economics and Policy, 2013).[20]

With respect to paediatric urology, the resistance pattern of uropathogens has been constantly evolving. When compared with the years 2002-2004, in 2009 the resistance rates of trimethoprim/sulfamethoxazole (TMP/SMX) for *E. coli* paediatric urinary tract infections (UTIs) increased in both boys (from 23% up to 31%) and girls (from 20% up to 23%). Also a ten-time increase in *E. coli* resistance to ciprofloxacin in boys (from 1% in 2002–2004 to 10% in 2009) and girls (from 0.6% to 4%) in paediatric UTIs was reported.[21] Moreover, paediatric hospitalizations for pyelonephritis in California increased from 17 per 100,000 children in 1985 to 31 per 100,000 children in 2006.[22]

There is often misuse of certain antibiotics in the outpatient treatment of paediatric UTIs. There has been a strong shift towards using the newer antibiotic classes, including macrolides and fluoroquinolones. There were fewer overall prescriptions for antibiotics in 2010 as compared to 1999, but the prescription for macrolides increased from 22% to 27%; similarly, the prescription for quinolones increased from 9% to 12%. Increased use of an antibiotic class can markedly accelerate the rise of bacterial resistance.[23]

Irrational empirical antibiotic therapy may contribute to increased morbidity and increased expenses due to the long durations of the antibiotic treatment and recurrent hospital admissions.[24] Based on clinical and in vitro studies, TMP/SMX should not be used empirically. However, data from the National Ambulatory Medical Care Survey suggests that around 50% of children were prescribed TMP/SMX for paediatric UTIs even though recent data suggests that most regions in the United States have resistance rates to TMP/SMX that exceed the approved levels for prescribing this antibiotic empirically.[25]

Recent examination of UTI resistance patterns has demonstrated that most UTIs are sensitive to narrow spectrum antibiotics, such as first-generation cephalosporins and urinary antiinfectives (nitrofurantoin). These underutilized antibiotics have demonstrated significantly low resistance rates over time.[26]

### Endoscopic Injection in Vesicoureteral Reflux

It is in the view of the strong yet fearful risk of development of antibiotic resistance which strongly increases the incidence of mortality and patients dying due to infections worldwide, that the question and the concept of an alternative mode of intervention (ie, surgical) arises in the patients with VUR. The various surgical options are – open surgery, laparoscopic and endoscopic injection at the ureteric orifice. With all of them, the underlying anomaly at the vesicoureteric junction is corrected. However, the endoscopic injection has certain advantages over the open surgery.

Surgical cure of VUR reduces the occurrence of pyelonephritis, though it has not been proven to reduce the existing renal injury. Patients with recurrent pyelonephritis and/or persistent reflux benefit most from surgery.[27]

The various theoretical advantages of laparoscopic approach to reflux repair include decreased hospital stay, decreased postoperative pain, smaller incisions, and faster recovery. It has efficacy similar to open surgery, with success rates of 88% to 100%, but technical difficulty, longer durations during the procedure and the probable risk of higher rate of complications including ureteral injury/obstruction, urine leak, and fistula, have prevented its widespread adoption.[28]

Endoscopic injection techniques prevent reflux by injecting a bulking substance to allow elevation and coaptation of the ureteral orifice. The various benefits of the endoscopic technique over open surgery are - outpatient procedure and in case of hospital admission, minimal duration of hospital stays, non-invasive and reduced patient morbidity.

An ideal injectable material must have the following characteristics - durable, effective, safe, inert, easily injectable, stable with time and must not migrate, biocompatible, non-antigenic and non-carcinogenic. Dextranomer/ hyaluronic acid (Dx/HA or Deflux®) was approved by the United States Food and Drug Administration in 2001 for the treatment of VUR Grades II to IV. Dextranomer/hyaluronic acid copolymer is a viscous gel consisting of two sugar-based molecules. The microspheres are suspended in non-animal stabilized hyaluronic acid. The microspheres are large in size (80–250 μm) and therefore less likely to embolize or migrate.[29]

In one of the earliest studies conducted by Stenberg (1995) in Sweden, the authors investigated the short-term (three months) and long-term (one year) effects of Deflux® implantation in 101 ureters with Grade III and Grade IV VUR. Three months later at voiding cystography, reflux had totally resolved in 68% of implants, had down-graded to Grades I and II in 13% of ureters, and was unchanged in 19% of ureters. No adverse reactions were noted. The results indicated that the dextranomer microspheres promote ingrowth of fibroblasts and generate new collagen. The authors concluded that the Deflux may represent a new and safe alternative to treatment of VUR in children.[30]

In one of the early studies, Puri (2003) prospectively evaluated the effectiveness of dextranomer/ hyaluronic acid copolymer in the endoscopic treatment of VUR. The reflux was completely corrected in 143 (86%) of the 166 ureters after a single endoscopic injection. No untoward effects were observed in these patients with the use of this copolymer as an endoscopic injectable material.[31]

Kim (2015) in their article relating to long-term follow-up in children treated with endoscopic injection retrospectively examined and analyzed 419 ureters of 243 patients. These patients underwent Deflux® injection therapy between September 2004 and September 2014. It was found that the Deflux® injection was highly efficacious with almost no complication for the anti-reflux procedure in children. The complete cure rates at three months, one year, and three years follow-up in the patients were 70.8%, 64.3%, and 65.6%, respectively. There was an extremely low recurrence rate of UTI and high probability of no VUR at three years if no VUR occurred at 1 year.[32]

Beetz (2002) evaluated the ongoing risk of UTIs in long-term follow-up of 158 young adults surgically treated for VUR in childhood. It was observed that in the entire long-term follow-up period, episodes of UTI developed in 66% of all patients, including 74% of female patients. Out of 46 pregnancies, symptomatic UTIs were observed in eight cases.[33]

Mor (2003) also reviewed patients who had surgical correction of VUR by ureteric reimplantation during childhood, and thus assessed their long-term outcome. In the 1970s, 322 children underwent surgical correction of VUR; these patients were followed-up for a long duration of 20 years. The follow-up focused on the incidence of UTIs, current renal function tests, complications during pregnancy, and the incidence of development of hypertension at least 20 years after surgery. In the study group, 49% had long-term urological complications. The incidence of UTIs was 43% in women and 24% in men, respectively. The onset of hypertension was detected in 6% of the patients during follow-up. There was development of renal scars, despite surgery, in 20% of the patients. Among 47 females who became pregnant, 28% reported UTIs during pregnancy. Thus, this study showed that even patients who were treated successfully by open surgery during their early life were prone to develop UTIs, progressive renal scarring, hypertension, and complications during pregnancy. The authors realized and emphasized that there is a need to establish a protocol for the long-term follow-up of such patients.[34]

Thus from several studies as mentioned above, it was realized that patients who have undergone open surgery for VUR in childhood are not free from complications in later life. However longterm follow up after endoscopic injection in VUR shows almost no complications and an extremely low rate of recurrence of UTI.[32]

In a systematic review to identify the role of Dextranomer/hyaluronic ccid for paediatric VUR, the authors searched the Cochrane Controlled Trials Register and other databases from 1990 to 2008 and found that the overall success rate with Deflux® injection was 77% after 3 months with variations existing among studies. It was also observed that increased VUR grade negatively affected success rates.[35]

### Conclusion

In view of the emerging landscape of antibiotic resistance in VUR in children, it would definitely not be recommended to prescribe long-term or repeated chemoprophylaxis in children. Among surgical options, endoscopic injection in these children is an option with minimum hospital stay, non-invasive nature and reliable success rates when injected appropriately. Thus, an increased use of the endoscopic injection (Deflux®) should be encouraged in children suffering from Grades II to IV VUR.

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