Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux

Medical Policy

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Description

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney and is most commonly seen in children. The primary management strategies have been use of prophylactic antibiotics to reduce urinary tract infections and, for higher grade disease, surgical correction of the underlying reflux. Injection of periureteral bulking agents is proposed as an alternative to surgical intervention.

Treatment of vesicoureteral reflux (VUR) is based on the assumption that VUR predisposes patients to urinary tract infections (UTIs) and renal infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract. Pyelonephritis causes renal scarring in as many as 40% of children, and extensive scarring may lead to renal insufficiency and hypertension. The period between first renal scarring from pyelonephritis and the development of hypertension or end-stage renal disease can be 30-40 years. (1)

In most cases, VUR is diagnosed during evaluation of UTIs. Approximately one-third of children with UTIs are found to have VUR. (2) The average age for the onset of UTI is 2 to 3 years, corresponding to the age when toilet training occurs. There also appears to be a genetic predisposition to VUR, and siblings may also be examined. The gold standard for diagnosis is voiding cystourography, a procedure that involves catheterization of the bladder. The severity of reflux is described by a grade, typically with the International Reflux Study Group grading system, which grades severity from I (reflux partway up the ureter) to V (massive reflux of urine up the ureter with marked tortuosity and dilation of the ureter and calyces). Determination of VUR grade is not exact, however, due to factors such as bladder pressure, which may vary at the time of measurement. In general, more severe reflux is associated with higher rates of renal injury, and less severe reflux (i.e., grade I and II) is associated with higher rates of spontaneous resolution and treatment success. (3, 4) Other factors found to be associated with the likelihood of spontaneous resolution of VUR and/or renal injury include age, sex, laterality, presence of renal scars, presence of voiding dysfunction, and history of UTI. (1)
Treatment strategies for VUR include bladder training, antibiotic prophylaxis, and surgical modification of the ureter to correct the underlying reflux. VUR is likely to resolve spontaneously over a period of 1–5 years; lower grades of reflux (i.e., grades I and II) are associated with a higher probability of spontaneous resolution. (3, 4) The decision to administer prophylactic antibiotic treatment includes the consideration of potential adverse effects of long-term antibiotic treatment, which can include allergic reactions and development of treatment-resistant bacteria resulting in breakthrough UTIs.

Open surgical treatment is typically reserved for patients with high-grade reflux (grades III and IV) or as salvage therapy for those who are noncompliant with antibiotic therapy or have breakthrough UTIs while receiving prophylactic therapy. Surgical management involves lengthening the intramural ureter by modification of the ureterovesical attachment with reimplantation of the ureter. Success rates for open surgery are reported to be greater than 95% and nearly 100% for patients with lower grades of reflux. In recent years, there have been advances in surgical technique, including use of a lower abdominal transverse incision that leaves a smaller scar. Combined with a reduction in the use of ureteral stents and prolonged catheterization; the changes have led to shorter hospital stays and reduced surgery-related morbidity. Moreover, surgeries can now be done on an outpatient basis. Surgery, however, still involves risks associated with anesthesia and potential complications, such as ureteral obstruction, infection, and bleeding. (1) Some centers have reported using laparoscopic antireflux surgery, but this is technically difficult and has not become widespread. Robotic-assisted laparoscopic methods are being developed to overcome some of the technical difficulties. (5)

Treatment of VUR remains controversial. There is a lack of good evidence that VUR actually increases the risk of pyelonephritis and renal scarring, and the long period of time before renal scarring, hypertension, and end-stage renal disease makes these serious conditions difficult to study. Moreover, VUR has a relatively high rate of spontaneous resolution, more than 60% over 5 years, so many children may not benefit from treatment. (6) An important challenge is to identify the subset of children most likely to benefit from VUR treatment. At present, in the absence of definitive answers on the utility of treating VUR or the best treatment option, antibiotic prophylaxis to prevent recurrent UTIs and surgery to treat the underlying reflux remain accepted management strategies.

The use of bulking agents in the treatment of VUR has been reported for more than 20 years and has been suggested as an alternative to either antibiotic or surgical therapy. Bulking agents can be injected into tissue around the ureteral orifices to minimize reflux. The STING procedure (subureteral transurethral injection) involves the endoscopic injection of a bulking agent into the submucosal bladder wall just below the ureteral opening. In the more recently used modified STING procedure, the needle is placed in the ureteral tunnel, and the bulking agent is injected into the submucosal intraureteral space. When successfully injected, the compound tracks along the length of the detrusor tunnel and establishes a coapted ureteral tunnel. This endoscopic procedure can be performed in an outpatient setting.

A variety of bulking agents have been tested for biocompatibility and absence of migration. Some of the compounds used in clinical studies are collagen (Contigen, Zyderm, Zyplast), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique®), calcium hydroxyapatite (Coaptite®), and dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA).

**Regulatory Status**

FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of FirstHealth OF THE CAROLINAS, INC.
In 2001, Deflux® received premarket application (PMA) approval from the U.S. Food and Drug Administration (FDA) for the “treatment of children with vesicoureteral reflux (VUR) grades II-IV.” Contraindications include patients with nonfunctioning kidney(s), duplicated ureters, active voiding dysfunction, and ongoing urinary tract infection.

Note: Polytetrafluoroethylene may migrate, causing serious adverse events; this agent is not FDA approved. Coaptite®, Macroplastique®, and Tegress® are categorized by the FDA as “Agent, Bulking, Injectable for Gastro-Urology Use.” Tegress was voluntarily withdrawn from the market by CR Bard as of January 31, 2007.

Policy

Periureteral bulking agents may be considered medially necessary as a treatment of vesicoureteral reflux grades II-IV when medical therapy has failed and surgical intervention is otherwise indicated.

The use of bulking agents as a treatment of vesicoureteral reflux in other clinical situations is considered investigational.

Policy Guidelines

The use of bulking agents is contraindicated in patients with non-functioning kidney(s), hutch diverticuli, duplicated ureters, active voiding dysfunction, and ongoing urinary tract infection.

Coding Issues:

CPT code 52327 would apply to the use of any bulking agent, including Deflux, to treat VUR:

52327: Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material.

Effective 1/1/09, there is a specific HCPCS code for Deflux:

L8604: Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies.

Bilateral treatment of VUR is typical, therefore, each of the above codes could be used twice.

Rationale

Treatment of vesicoureteral reflux (VUR) with periurethral bulking agents is proposed as: 1) an alternative to other types of surgery for patients with high-grade VUR (predominantly grades III and IV) who have failed or are noncompliant with prophylactic antibiotics; and 2) an alternative to prophylactic antibiotics for patients with lower-grade or high-grade VUR. Appropriate outcomes for the comparison of bulking agents and other types of surgery are resolution of reflux and reduction in the rate of urinary tract infections (UTIs) and pyelonephritis. Since prophylactic antibiotic use does not treat the underlying reflux, reduction in the rate of UTIs and pyelonephritis are reasonable outcomes for studies comparing antibiotics and bulking agents. Differences in morbidity are also important outcomes for both proposed uses.
An initial literature search was performed in 2005. The policy was updated regularly with a literature review using MEDLINE; most recently, the literature was searched from August 2011 through August 2012. Following is a summary of key literature to date on use of periureteral bulking agents to treat VUR.

**Efficacy of Bulking agents for VUR**

The Cochrane Library conducted a review of randomized controlled trials (RCTs) on treatments for VUR. (7) The review was available at the time the policy was developed, and it was updated most recently in 2011. It addressed a variety of interventions including long-term antibiotic prophylaxis, open surgery, and use of bulking agents. The Cochrane review had limited ability to evaluate the efficacy of bulking agents because it combined studies on open surgery and bulking agents in the analysis. The review, however, is useful for examining the assumption that VUR increases the risk of complications.

The updated review included 20 trials with a total of 2,324 children. No statistically significant differences were found in the overall risk of UTI or renal parenchymal injury between groups treated with surgery or bulking agents plus antibiotics versus antibiotic prophylaxis alone at any time point between 1 and 24 months For example, a meta-analysis of 5 trials that evaluated repeat positive urine culture by 1-2 years found a non-significant risk ratio (RR) of 0.89 (95% confidence interval [CI]: 0.55 to 1.44). In addition, a meta-analysis of 4 trials that evaluated the outcome of new renal parenchymal defects at 4-5 years after treatment calculated a pooled RR of 1.09 (95% CI: 0.79 to 1.49). One statistically significant finding was a reduction in febrile UTI by 5 years with surgery or bulking agent treatment compared to antibiotics alone; in a pooled analysis of 2 studies (449 children), RR: 0.43; 95% CI: 0.27 to 0.70. These findings challenge the assumptions underlying the treatment of VUR, since one would expect a reduction in UTI if the hypothesis is correct that VUR is a modifiable risk factor for UTI and renal parenchymal damage.

Following is a description of representative published RCTs evaluating periureteral bulking agents for treatment of VUR.

Capozza and Caione reported on the results of a study of 61 children with VUR (grades II to IV) who were randomly assigned to receive an endoscopic subureteral implantation (n=40) of Deflux or 12 months of antibiotic prophylaxis (n=21). (8) Entry criteria included grades II to IV reflux present for at least 6 months. The antibiotic therapy was not specified and presumably was variable. It was not reported whether patients had been receiving antibiotic therapy during the preceding 6 months and experienced breakthrough UTIs, were noncompliant, or showed no evidence of spontaneous resolution of VUR. Therefore it is unknown whether the Deflux treatment was primarily considered an alternative to medical therapy or to surgical therapy. In part, due to the small numbers in the antibiotic control group, the distribution of the different grades of VUR was different in the 2 groups. Outcomes included improvement in reflux grade and measures of renal function; incidence of UTIs was not reported. The only statistically significant outcome reported was the improvement in reflux grade at month 12, with 69% of those in the Deflux group reporting a reflux grade of I or less, compared to only 38% in the antibiotic group. However, these results are not surprising, since antibiotic therapy itself is not intended to improve reflux grade but simply to sterilize the urine while awaiting the spontaneous resolution of VUR. Therefore, the only conclusion is that Deflux results in a higher incidence of VUR resolution compared to spontaneous resolution.
Findings from the Swedish Reflux trial in children were published in 2010. (9-12) This non-blinded multicenter study included 203 children (128 girls and 75 boys) between the ages of 1 and 2 years with grade III to IV reflux. Most of the participants (194, 96%) were identified after a symptomatic UTI. Recruitment was more difficult than expected, and enrollment was stopped after 6 years. Participants were randomly assigned to 1 of 3 groups: antibiotic prophylaxis (n=69), endoscopic treatment with Deflux (n=66), or surveillance only (n=68). Participants were not required to have failed antibiotic prophylaxis; thus the trial evaluated injection of a bulking agent as an alternative to antibiotic therapy. The study aimed to simulate clinical practice, i.e., prophylactic antibiotics were prescribed without monitoring compliance, rather than ensuring that study participants took a known dose of antibiotics. Primary study outcomes included VUR status, and rates of febrile UTI and kidney damage after 2 years. Sixty-four of 66 patients randomly assigned to endoscopy received treatment. Fourteen of 19 patients with still dilating VUR after 1 injection received a second injection; 2 patients received a third injection. The investigators reported that complications occurred in 6 of the 64 (9%) individuals who received endoscopic treatment. Overall, 187 participants (92%) completed at least 6 of the 8 follow-up visits; analysis was intention to treat.

Two-year cystourethrography was done in 185 of the 203 (91%) patients. Findings from voiding cystourethrography were that VUR had resolved in 9 of 68 (13%) patients in the prophylaxis group, 20 of 52 (38%) in the endoscopy group, and 10 of 65 (15%) in the surveillance group. The proportion of patients in the 3 groups whose VUR was downgraded to grade I or II was 18 of 68 (26%), 17 of 52 (33%) and 21 of 65 (32%), respectively. There was a significantly greater proportion of patients whose VUR had resolved or had been downgraded in the endoscopy group compared to the prophylaxis (p=0.0002) and surveillance groups (p=0.003), but no statistically significant differences were found between the prophylaxis and surveillance groups. Thirteen patients (20% of the 66 patients randomly assigned to endoscopy) whose VUR had initially resolved or been downgraded experienced recurrences and had stage III or IV VUR at 2 years. Rates of febrile UTI recurrence during follow-up were dramatically higher in girls (42 of 128, 33%) than boys (7 of 75, 9%). Febrile UTI rates by treatment group in girls were 8 of 43 (19%), 10 of 43 (23%), and 24 of 42 (57%), respectively, in the prophylaxis, endoscopic, and surveillance groups. Rates were significantly higher in the surveillance group than either the prophylaxis group (p=0.002) or the endoscopic group (p=0.14); rates did not differ significantly in the prophylaxis versus the endoscopic groups. Rates of febrile UTIs in boys were 2 of 26 (8%) in the prophylaxis group, 4 of 23 (17%) in the endoscopic group, and 1 of 26 (4%) in the surveillance group; there were no statistically significant differences between groups. A total of 24 patients were found to have new renal damage in a previously unscarred area, 4 of 68 (6%) on prophylaxis, 8 of 65 (12%) in the endoscopy group, and 12 of 68 (18%) in the surveillance group. (Two children were not evaluated for this outcome.) The rate of new renal damage did not differ significantly among groups. After stratifying findings by gender, the sample sizes in reported analyses were relatively small. There may have been insufficient power to evaluate some of the outcomes of interest, e.g., kidney damage and febrile UTIs. Moreover, findings might not be applicable to children outside of the restricted age range included in the study and to those with lower-grade VUR. Larger studies with a more representative sample of children with VUR are needed to further evaluate the effectiveness of this treatment.

A systematic review published in 2010 identified randomized trials and observational studies evaluating dextranomer/hyaluronic acid (Dx/HA) treatment for pediatric VUR. (13) A total of 47 studies, mainly retrospective case series, met eligibility criteria. A key inclusion was that studies report the postoperative success rate after a single injection of Dx/HA. Success was defined as resolution of VUR and could also include downgrading to grade 1 VUR. Of 7,303 ureters
injected with Dx/HA, 5,633 (77%) were considered treatment successes. There were higher rates of success in children with lower-grade reflux compared to those with high-grade reflux. For example, the 164 children whose preoperative VUR was grade 1 had an 89% success rate compared to a 59% success rate among the 1,109 children with initial grade IV VUR.

**Comparative efficacy of different bulking agents**

Oswald and colleagues randomly assigned 72 children with VUR to receive either Deflux or Macroplastique in addition to antibiotic prophylaxis. (14) Entry criteria included grades II to IV reflux (International Reflux Study Group grading system). Since all patients continued to receive antibiotic therapy, presumably, the bulking procedure was primarily considered an alternative to surgical reimplantation of the ureter. However, the patient selection criteria do not indicate whether patients had failed prior antibiotic therapy or had unresolved VUR. Correction of underlying VUR was similar in the 2 groups.

Kim and colleagues randomized 85 children aged 2-15 years with VUR (grades II-V) to receive subureteral injections of Macroplastique (n=42) or Deflux (n=43). (15) Eligibility included breakthrough UTI in addition to persistent VUR; most patients had started immediately on antibiotic prophylaxis after diagnosis (exact number not reported). Seventy-three of 85 children (86%) were available for the 3-month follow-up. The cure rate, defined as no evidence of reflux, was 69% in the Macroplastique group and 55% in the Deflux group; the difference between group was statistically significant, p<0.05. This study did not include a group of patients who received a treatment other than periureteral injection of bulking agents.

**Adverse Events**

According to case series data, injection of periureteral bulking agents is associated with low morbidity rates. Temporary postoperative ureteral obstruction may occur in less than 0.7% of patients following injection of bulking agents; this can be treated with ureteral stenting until the problem resolves. (16) In comparison, an average 2% (range, 0% to 9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. (17) A large series published in 2012 by Puri and colleagues retrospectively reported on 1,551 children injected with dextranomer/hyaluronic acid for high-grade VUR. (18) The only reported procedure-related complication was hematuria lasting up to 12 hours in 3 patients. There was no evidence of delayed vesicoureteral junction obstruction. Febrile urinary tract infections occurred in 69 (5%) of patients during follow-up; the median length of follow-up was 5.6 years.

**Summary**

There are no head-to-head, randomized, controlled trials comparing periureteral bulking agents to other types of surgery used to treat VUR. However, the available evidence suggests that rates of reflux resolution are reasonably high with bulking agent injection, and morbidity rates tend to be lower than with other surgeries. Thus, the use of bulking agents to treat VUR as an alternative to other surgical methods is considered medically necessary.

To date, there is one head-to-head randomized trial comparing periureteral bulking agents to antibiotic prophylaxis; the study included a selected population and had a relatively small sample size. Additional, larger studies are needed before conclusions can be drawn about the efficacy of periureteral bulking agents as first-line treatment for patients with VUR. Therefore, periureteral bulking agents are considered investigational as an alternative to antibiotic prophylaxis.
Practice Guidelines and Position Statements

In 2012, The European Association of Urology (EAU) published a guideline on the diagnosis and treatment of VUR in children. (19) The EAU recommends continuous antibiotic prophylaxis as initial treatment for children diagnosed with VUR in the first year of life and for children age 1-5 years who present with high-grade VUR. For children age 1-5 with lower grade VUR and no symptoms, surveillance without antibiotic prophylaxis is considered to be a reasonable option. The document states that surgical correction is a treatment option for patients with persistent symptoms and that endoscopic injection of bulking materials can have satisfactory results in children with lower grades of VUR.

In 2010, the American Urological Association published an updated guideline on management of primary VUR in children. (20) They recommend that patients older than 1 year who have a febrile breakthrough UTI while receiving continuous antibiotic prophylaxis be considered for either open surgery or endoscopic injection of bulking agents. Specific bulking agents mentioned were Deflux and Macroplastique. The guideline was based on a review of the evidence, but the authors acknowledged the lack of robust randomized controlled trials.

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