

## Medical Policy



### Title: Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux (VUR)

#### Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>With vesicoureteral reflux who have failed medical therapy and are eligible for surgery</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Endoscopic treatment with periureteral bulking agents</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Ureteral reimplantation surgery</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With vesicoureteral reflux who have not failed medical therapy and may be ineligible for surgery</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Endoscopic treatment with periureteral bulking agents</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Antibiotic prophylaxis</li> <li>Ureteral reimplantation surgery</li> <li>Surveillance only</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Treatment-related morbidity</li> </ul>

## **DESCRIPTION**

Most commonly seen in children, vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney. The primary management strategies have been 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.

## **OBJECTIVE**

The objective of this policy is to determine whether endoscopic treatment with periureteral bulking agents improves the net health outcome in individuals who have vesicoureteral reflux and (a) have failed medical therapy and are eligible for surgery or (b) have not failed medical therapy and may be ineligible for surgery.

## **BACKGROUND**

### **Vesicoureteral Reflux**

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 to 40 years.<sup>1</sup>

### **Diagnosis**

In most cases, VUR is diagnosed during evaluation of UTIs. Approximately one third of children with UTIs are found to have VUR.<sup>2</sup> The average age for UTI onset 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 criterion standard for diagnosis is voiding cystourethrography, 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 (ie, grade I and II) is associated with higher rates of spontaneous resolution and treatment success.<sup>3,4</sup> 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.<sup>1</sup>

### **Treatment**

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 1 to 5 years; lower grades of reflux (ie, grades I and II) are associated

with a higher probability of spontaneous resolution.<sup>3,4</sup> The decision to administer prophylactic antibiotic treatment includes consideration of potential adverse events 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.<sup>1</sup> 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.<sup>5</sup>

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.<sup>6</sup> 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.

### *Bulking Agents*

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 antibiotic and 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® [Allergan, Coolock, Ireland; note: this product is no longer commercially available], Zyderm®, Zyplast® [Collagen Corp.]), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique), calcium hydroxyapatite (Coaptite), dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA), and polyacrylamide hydrogel (Bulkamid® [Contura International A/S]).

### 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.<sup>7</sup> In comparison, on average, a 2% (range, 0%-9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation.<sup>8</sup> A large series published by Puri et al (2012) retrospectively reported on 1551 children injected with Dx/HA for high-grade VUR.<sup>9</sup> 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 UTIs occurred in 69 (5%) patients during follow-up; median follow-up was 5.6 years. Dwyer et al (2013) compared the rate of febrile UTIs in 2 cohorts of patients with VUR.<sup>10</sup> The incidence of febrile UTI did not differ significantly between patients who had ureter reimplantation (8% [16/210 cases]) and those who had endoscopic injections of Dx/HA (4% [4/106 patients]) (p=0.24).

### **REGULATORY STATUS**

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), active voiding dysfunction, and ongoing urinary tract infection. Duplicated ureters were initially considered a contraindication to Deflux treatment, but this was changed to a precaution in 2007.

Note: Polytetrafluoroethylene may migrate, causing serious adverse events; this agent is not FDA approved. Coaptite® (Merz Aesthetics, Raleigh, NC), Macroplastique®, and Tegress® (CR Bard, Murray Hill, NJ) 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.

FDA product code: LNM.

## **POLICY**

- A. Periureteral bulking agents may be considered **medically necessary** as a treatment of vesicoureteral reflux grades II–IV when medical therapy has failed and surgical intervention is otherwise indicated.
  
- B. The use of bulking agents as a treatment of vesicoureteral reflux in other clinical situations is considered **experimental / investigational**.

## **Policy Guidelines**

The use of bulking agents is contraindicated in patients with nonfunctioning kidney(s), Hutch diverticuli, active voiding dysfunction, and ongoing urinary tract infection.

## **RATIONALE**

This policy's most recent literature update was performed through June 7, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **Efficacy of Bulking Agents for vesicoureteral reflux**

Treatment of vesicoureteral reflux (VUR) with periurethral bulking agents is proposed for 2 indications: (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 low-grade or high-grade VUR (ie, those who have not failed medical treatment and may be ineligible for surgery).

### **Clinical Context and Therapy Purpose**

The purpose of endoscopic treatment with periureteral bulking agents in patients with vesicoureteral reflux who have either failed medical therapy and are eligible for surgery or not

failed medical therapy and may be ineligible for surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of endoscopic treatment with periureteral bulking agents improve the net health outcome in patients with vesicoureteral reflux who may or may not have failed medical therapy and, consequently, are eligible or ineligible for surgery?

The following PICOTS were used to select literature to inform this review.

### Patients

The relevant populations of interest are patients with vesicoureteral reflux who have either failed medical therapy and are eligible for surgery or have not failed medical therapy and may be ineligible for surgery. Primary vesicoureteral reflux is the most common type of VUR and occurs as a result of a congenitally incompetent ureterovesical junction. Children younger than 2 years of age, white ethnicity, and female sex are risk factors for VUR. Children with partial or complete duplicated ureters are also at increased risk of VUR.

### Interventions

The therapy being considered is endoscopic treatment with periureteral bulking agents.

### Comparators

The following therapies and practices are currently being used to make decisions about vesicoureteral reflux: ureteral reimplantation surgery for patients who have either failed medical therapy and are eligible for surgery or antibiotic prophylaxis, ureteral reimplantation surgery, and surveillance only for those who have not failed medical therapy and may be ineligible for surgery.

### Outcomes

The general outcomes of interest are a reduction in urinary tract infections (UTIs), reductions in the incidence of pyelonephritis, and treatment-related adverse events.

Appropriate outcomes for the comparison of bulking agents and other types of surgery are the resolution of reflux and reduction in the rate of UTIs and pyelonephritis. Because prophylactic antibiotic use does not treat the underlying reflux, reduction in the rate of UTIs and pyelonephritis are reasonable outcomes for studies comparing antibiotics with bulking agents. Differences in morbidity are also important outcomes for both proposed uses.

### Timing

Bulking agents may or may not be curative, and follow-up injection may be necessary within 6 months. Beneficial effects may last between 3 and 12 months.

### Setting

Injectable bulking agents are administered under local anesthesia in an outpatient setting.

### Systematic Reviews

A Cochrane review by Nagler et al (2011) included RCTs evaluating treatments for VUR.<sup>11</sup> Reviewers addressed a variety of interventions including long-term antibiotic prophylaxis, open surgery, and the use of bulking agents. Reviewers' decision to combine studies on open surgery

and bulking agents limited ability to analyze the efficacy of bulking agents. The review, however, is useful because it examines the assumption that VUR increases the risk of complications. This Cochrane review selected 20 trials (total N=2324 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 and antibiotic prophylaxis alone at any time point between 1 and 24 months. For example, a pooled analysis of data from 5 trials that evaluated repeat positive urine culture at 1 to 2 years found a nonsignificant relative risk of 0.89 (95% confidence interval, 0.55 to 1.44). In addition, a pooled analysis of 4 trials that evaluated the outcome of new renal parenchymal defects at 4 to 5 years after treatment calculated a pooled relative risk of 1.09 (95% confidence interval, 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 with antibiotics alone in a pooled analysis of 2 studies (449 children) (relative risk, 0.43; 95% confidence interval, 0.27 to 0.70). These findings challenge the assumptions underlying the treatment of VUR because 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.

A systematic review by Routh et al (2010) identified randomized trials and observational studies evaluating dextranomer/hyaluronic acid (Dx/HA) copolymer treatment for pediatric VUR.<sup>12</sup> A total of 47 studies, mainly retrospective case series, met eligibility criteria. A key inclusion criterion 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 I VUR. Of 7303 ureters injected with Dx/HA, 5633 (77%) were considered treatment successes. There were higher rates of success in children with low-grade reflux than in those with high-grade reflux. For example, the 164 children whose preoperative VUR was grade I had an 89% success rate compared with a 59% success rate among the 1109 children with initial grade IV VUR.

#### Randomized Controlled Trials

##### *Periureteral Bulking Agents vs Surgery*

The first RCT comparing periureteral bulking agents with ureteral reimplantation (UR) was published by Garcia-Aparicio et al (2013). They randomized 41 children older than 1 year of age with VUR grades I to IV to endoscopic treatment with Dx/HA (n=22) or UR (n=19).<sup>13</sup> Indications for surgery included recurrent UTIs, persistent VUR after 2 years of antibiotic prophylaxis, impairment of renal function, or another type of impairment due to VUR. Thirty-five refluxing ureters were treated with bulking agents, and 32 refluxing ureters were treated with UR. One year after treatment, 32 (91.4%) of 35 ureters in the Dx/HA group and 32 (100%) of 32 ureters in the surgical reimplantation group were cured; the difference between groups was not statistically significant (p=0.23). Findings were similar at final follow-up. At 5 years, 30 (85.7%) of 35 ureters in the Dx/HA group and 100% in the UR group were free of VUR (p=0.48). One patient in the Dx/HA group and 2 patients in the UR group experienced treatment complications. Two patients in the Dx/HA group and none in the UR group experienced fevers posttreatment. Rates of complications and adverse events did not differ significantly between groups. Trial results supported a finding of no large differences between the 2 treatments, but the study was not powered to detect smaller differences in outcomes and was also likely too small to detect differences in complications and adverse events.

##### *Periureteral Bulking Agents vs Antibiotic Prophylaxis*

Capozza and Caione (2002) reported on the results of 61 children with VUR (grades II-IV) who were randomized to an endoscopic subureteral implantation (n=40) of Deflux or 12 months of

antibiotic prophylaxis (n=21).<sup>14</sup> Entry criteria included grades II, III, or IV reflux present for at least 6 months. The antibiotic therapy was not specified and presumably varied. 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. Partly due to the small numbers in the antibiotic control group, the distribution of the different grades of VUR differed between 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 an improvement in reflux grade at month 12, with 69% of those in the Deflux group reporting a reflux grade of I or less—compared with only 38% in the antibiotic group. However, these results should not be surprising, because antibiotic therapy 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 than spontaneous resolution.

Findings from the Swedish Reflux Trial in children were published by Brandstrom and colleagues (2010).<sup>15-18</sup> This nonblinded multicenter study included 203 children (128 girls, 75 boys) between the ages of 1 and 2 years with grade III, III, or IV reflux. Participants were not required to have failed antibiotic prophylaxis; thus, the trial evaluated injection of a bulking agent as an alternative to antibiotic therapy. Most participants (194 [96%]) were identified after a symptomatic UTI. Recruitment was more difficult than expected, and enrollment was stopped after 6 years. Participants were randomized to 1 of 3 groups: antibiotic prophylaxis (n=69), endoscopic treatment with Deflux (n=66), or surveillance only (n=68).

The trial aimed to simulate clinical practice, ie, 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 randomized to endoscopy received treatment. Fourteen of 19 patients with ongoing dilating VUR after 1 injection received a second injection; 2 patients received a third injection. Complications occurred in 6 (9%) of the 64 individuals who received endoscopic treatment. Overall, 187 (92%) participants completed at least 6 of the 8 follow-up visits; analysis was intention to treat. Two-year cystourethrography was done in 185 (91%) of the 203 patients. Voiding cystourethrography findings indicated that VUR had resolved in 9 (13%) of 68 patients in the prophylaxis group, in 20 (38%) of 52 in the endoscopy group, and in 10 (15%) of 65 in the surveillance group. The proportion of patients in the 3 groups whose VUR was downgraded to grade I or II were 18 (26%) of 68, 17 (33%) of 52, and 21 (32%) of 65, respectively. There was a significantly greater proportion of patients whose VUR had resolved or had been downgraded in the endoscopy group than in the prophylaxis ( $p<0.001$ ) and the surveillance groups ( $p=0.003$ ). Thirteen (20%) of the 66 patients randomized to endoscopy whose VUR had initially resolved or been downgraded experienced recurrences and had stage III or IV VUR at 2 years.

Febrile UTI rates by treatment group in girls were 8 (19%) of 43, 10 (23%) of 43, and 24 (57%) of 42, 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 between the prophylaxis and the endoscopic groups. Rates of febrile UTI recurrence during follow-up were dramatically higher in girls (42/128

[33%]) than in boys (7/75 [9%]). The rate of new renal damage did not differ significantly among groups.

After stratifying findings by sex, the sample sizes in reported analyses were relatively small. For this reason, the study might have been insufficiently powered to evaluate some of the outcomes of interest (eg, kidney damage, febrile UTIs). Moreover, findings might not be applicable to children outside of the restricted age range evaluated or to those with lower grade VUR. Larger studies with a more representative sample of children with VUR are needed to evaluate the effectiveness of this treatment further.

#### Comparison Among Bulking Agents

Three RCTs have compared Deflux with Macroplastique for treatment of VUR in children. An earlier study by Oswald et al (2002) found similar rates of reflux correction in the 2 groups; however, more recent RCTs have found higher success rates with Macroplastique than with Deflux. Studies varied in their eligibility criteria (eg, grade of VUR, previous use of antibiotics). The RCTs are described next.

Oswald et al (2002) randomized 72 children with VUR to Deflux or Macroplastique in addition to antibiotic prophylaxis.<sup>19</sup> Eligible children had grade II, III, or IV reflux (International Reflux Study Group grading system). Because all patients continued to receive antibiotic therapy, the bulking procedure would have been primarily considered an alternative to surgical reimplantation of the ureter; however, patient selection criteria do not indicate whether patients had failed prior antibiotic therapy or had unresolved VUR. Three months postinjection, VUR was corrected in 50 (86%) of 58 ureters in the Macroplastique group and in 40 (71%) of 56 ureters in the Deflux group; the difference between groups was not statistically significant. Rates of maintaining reflux correction at 1 year were also similar in both groups.

Kim et al (2011) randomized 85 children ages 2 to 15 years with VUR (grades II-V) to subureteral injections of Macroplastique (n=42) or Deflux (n=43).<sup>20</sup> Eligibility included breakthrough UTI and persistent VUR; most patients (exact number not reported) had started immediately on antibiotic prophylaxis after diagnosis. Seventy-three (86%) of 85 children 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 groups was statistically significant, favoring Macroplastique (p<0.05).

An RCT by Moore and Bolduc (2014) randomized 275 children (median age, 50 months) with grade I, II, III, IV, or V VUR to endoscopic treatment with Macroplastique or Deflux.<sup>21</sup> Unlike previous trials, the trial included patients with grade I VUR (9% of ureters) as well as higher grade disease; results were not stratified by VUR grade. Previous endoscopic treatment of VUR was an exclusion criterion but previous use of antibiotics was not reported. Three months after a single injection of bulking agents, VUR was corrected in 104 (85%) of 122 patients in the Macroplastique group and in 101 (76%) of 133 patients in the Deflux group. As in the Kim trial, the difference between groups was statistically significant, favoring Macroplastique (p<0.05).

#### Children with Duplicated Ureters

No controlled studies have been published comparing bulking agents with other treatments in children with duplicated ureters. However, several case series are available, and these uncontrolled studies suggest reasonable response rates and do not report high complication rates in this

population. Hunziker et al (2013) published a case series of 123 children with complete duplex systems who were treated with Dx/HA for grade II, III, IV, or V VUR.<sup>22</sup> The mean age of participants was 3 years (range, 1 month to 12 years). Complete duplicated ureters were unilateral in 100 (81%) patients and bilateral in the remaining 13. A total of 136 refluxing ureteral units were treated with endoscopic injections of Dx/HA. Three months after treatment, children were evaluated using voiding cystourethrography and bladder ultrasound. The rate of VUR resolution after 1 injection was 68.4% (93/136 ureters). VUR resolved in an additional 35 (25.7%) ureters after a second injection and in the remaining 8 (5.9%) ureters after a third injection. There was 1 complication associated with the endoscopic injections, which was a case of frank hematuria. No patients needed ureteral reimplantation, and there was no evidence on ultrasound of delayed vesicoureteral junction obstruction. Five (4%) patients developed febrile UTIs during follow-up.

Molitierno et al (2008) included 52 children with duplex ureters who had grade II, III, IV, or V VUR.<sup>23</sup> Overall, VUR was cured in 44 (85%) of 52 patients after 1 or 2 treatments with Dx/HA. Lackgren et al (2003) evaluated 68 children with duplex ureters and VUR.<sup>24</sup> Forty-three (63%) children had a positive response to treatment, defined as having their reflux resolve to grade 0 or I. There were no complications associated with treatment. Seventeen (25%) children required open surgery.

### **SUMMARY OF EVIDENCE**

For individuals who have VUR who have failed medical therapy and are eligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, and treatment-related morbidity. Overall, studies have reported similar rates of reflux resolution compared with ureteral reimplantation surgery and the body of evidence would suggest that morbidity rates are similar or lower with bulking agents. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have VUR who have not failed medical therapy and may be ineligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, and treatment-related morbidity. The randomized controlled trials, which had relatively small sample sizes in each arm, compared periureteral bulking agents with antibiotic prophylaxis and/or surveillance only and reported mixed findings. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **PRACTICE GUIDELINES AND POSITION STATEMENTS**

#### European Association of Urology

In 2012, The European Association of Urology (EAU) published a guideline on the diagnosis and treatment of VUR in children.<sup>25</sup> 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.

American Urological Association

In 2010, the American Urological Association published an updated guideline on management of primary VUR in children.<sup>26</sup> 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 trial data.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

The U.S. Preventive Services Task Force has not addressed use of injectable bulking agents to treat VUR.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1.** Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT02771035	A Prospective Study Comparing the Success Rate of Injection of (DefluxR) Versus (VantrisR) for VUR in children	100	Dec 2015 (unknown)

NCT: national clinical trial.

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

CPT/HCPCS

- 52327 Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material
- L8604 Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies

- CPT code 52327 would apply to the use of any bulking agent, including Deflux, to treat VUR.
- There is a specific HCPCS code for Deflux: L8604.
- Bilateral treatment of VUR is typical; therefore, each of the above codes could be used twice.

ICD-10 Diagnoses

- N13.71 Vesicoureteral-reflux without reflux nephropathy
- N13.721 Vesicoureteral-reflux with reflux nephropathy without hydroureter, unilateral
- N13.731 Vesicoureteral-reflux with reflux nephropathy with hydroureter, unilateral
- N13.732 Vesicoureteral-reflux with reflux nephropathy with hydroureter, bilateral
- N13.9 Obstructive and reflux uropathy, unspecified

**REVISIONS**

08-17-2010	Updated Description section.
	In Policy Section: <ul style="list-style-type: none"> <li>▪ Liberalized policy Form:                      "Deflux® is medically necessary for the treatment of vesicoureteral reflux."</li> </ul> To: "Periureteral bulking agents may be considered medically 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 experimental / investigational."
	In Coding Section: <ul style="list-style-type: none"> <li>▪ Added HCPCS Codes: L8603, L8604</li> <li>▪ Removed CPT Code: 51715</li> </ul>
	Added Rationale Section
	Updated References
01-28-2011	Updated Rationale Section.
	Updated Reference Section.
12-31-2013	Policy reviewed.
	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Added ICD-10 Diagnosis (<i>Effective October 1, 2014</i>)</li> </ul>
	Updated Reference section.
01-08-2016	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ Added Policy Guidelines.</li> </ul>
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Added bulleted CPT and HCPCS descriptions.</li> </ul>
	Updated References section.
10-13-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Updated coding bullets.</li> </ul>
10-01-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Removed statement, "These diagnoses are otherwise subject to medical policy as stated above."</li> <li>▪ Removed ICD-9 codes.</li> </ul>
	Updated References section.

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