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

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Related Policies (if applicable)
SUR710.008 Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Disclaimer

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Coverage

Periureteral bulking agents **may be considered medically necessary** as a treatment of vesicoureteral reflux (VUR) grades II-IV when open surgical intervention is otherwise indicated.

The use of bulking agents as a treatment of VUR in any other clinical situations **is considered experimental, investigational and/or unproven.**

Policy Guidelines

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

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 (UTIs) and, for higher grade disease, surgical correction of the underlying reflux. Injection of periureteral bulking agents is proposed as an alternative to surgical intervention.

Vesicoureteral Reflux

Vesicoureteral reflux predisposes patients to 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) Although the exact prevalence of VUR in the general population is unknown, a meta-analysis of more than 250 articles revealed its occurrence in 31.1% of children who were evaluated for a UTI and 17.2% in those with normal kidneys who underwent a voiding cystourethrogram for other indications, such as hydronephrosis. (2)

Diagnosis

In most cases, VUR is diagnosed after a febrile UTI episode or abnormality seen on ultrasound imaging. (3) Approximately one-third of children with UTIs are found to have VUR. (4) 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; therefore, siblings may also be examined.

The criterion standard for diagnosis is voiding cystourethrography, a procedure that involves catheterization of the bladder. According to the 2011 American Academy of Pediatrics guideline on the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months of age (reaffirmed in 2016), voiding cystourethrography should not be performed routinely after the first febrile UTI. (5) Voiding cystourethrography is indicated if renal and bladder ultrasonography reveals hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances. 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. (6, 7) Other factors found to be associated with the likelihood of spontaneous resolution of VUR and/or renal injury include age, sex, laterality, the presence of renal scars, the presence of voiding dysfunction, and history of UTI. (1)

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 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, 6, 7) 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. Advances in surgical technique, including use of a lower abdominal transverse incision, have led to smaller scars. 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 not widespread. Robotic-assisted laparoscopic methods are being developed to overcome some of the technical difficulties. (8)

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 (>60% over 5 years), so many children may not benefit from treatment. (9) An important challenge is to identify the subset of children most likely to benefit from VUR treatment. (3) 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 is suggested as an alternative to 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 modified STING procedure, the needle is placed in the ureteral tunnel, and the bulking agent is injected into the submucosal intraurethral space. When successfully injected, the compound tracks along the length of the detrusor tunnel and establishes a coated ureteral tunnel. More recently, the HIT (hydrodistension of the ureteric orifice and injection of bulking agents in the mid to distal submucosal tunnel at the 6 o'clock position) and double HIT (modified HIT with proximal and

distal intraluminal submucosal injections) techniques have gained favor; a meta-analysis revealed that overall VUR resolution was 82.5% with HIT as compared to 71.4% with STING (p<.00001). (3, 10) These endoscopic procedures can be performed in an outpatient setting.

A variety of bulking agents have been tested for biocompatibility and absence of migration. Some compounds used in clinical studies are:

- Collagen (Contigen® [Allergan, Coolock; note: this product is no longer commercially available], Zyderm® and Zyplast® [use discontinued due to immune reaction concerns]) (11);
- Polytetrafluoroethylene paste (Teflon) [use discontinued due to concerns regarding particle migration] (11);
- Polydimethylsiloxane (Macroplastique®) [use discontinued due to concerns of malignant potential] (11);
- Calcium hydroxyapatite (Coaptite®);
- Dextranomer/hyaluronic acid copolymer (Deflux®, Dexell®, or Dx/HA);
- Polyacrylamide hydrogel (Bulkamid® [Axonics]); and
- Polyacrylate-polyalcohol copolymer (Vantris® [Promedon]).

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. (12) In comparison, on average, a 2% (range, 0%-9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. (13) In 2019, Friedmacher and Puri estimated the incidence of ureteral obstruction following endoscopic injections of various substances (i.e., Dx/HA, polyacrylate polyalcohol, polydimethylsiloxane, calcium hydroxyapatite, polytetrafluoroethylene, or collagen) in 25 publications. (14) Results revealed ureteral obstruction to be a rare complication after endoscopic correction of VUR, generally occurring in less than 1% of treated cases independent of the injected substance, volume, and technique.

A large series published by Puri et al. (2012) retrospectively reported on 1551 children injected with Dx/HA for high-grade VUR. (15) 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. (16) 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). Lightfoot et al. (2019) evaluated long-term outcomes after Dx/HA injection for primary VUR in 99 patients (median follow-up: 8.4 years). (17) Results revealed that a secondary surgery was performed in 13 (13.1%) patients, which was most commonly a repeat Dx/HA injection. Only 3 (3%) patients required open or laparoscopic surgery after Dx/HA injection. Additionally, of the 83 (84.7%) patients reporting ≥1 febrile UTIs preoperatively, only 9 (10.8%) reported postoperative occurrence of febrile UTIs.

Regulatory Status
In 2001, Deflux® was approved by the U.S. Food and Drug Administration (FDA) through the premarket application (PMA) process for the "treatment of children with vesicoureteral reflux (VUR) grades II-IV" and remains the only FDA-approved bulking agent for VUR. (11) Contraindications include patients with nonfunctioning kidney(s), Hutch diverticulum, ureterocele, active voiding dysfunction, and ongoing UTI. Duplicated ureters were initially considered a contraindication to Deflux® treatment, but this was changed to a precaution in 2007.

FDA product code: LNM.

Rationale

Medical policies 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 two 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 lower-grade or high-grade VUR (i.e., those who have not failed medical treatment and may be ineligible for surgery).

<u>Clinical Context and Therapy Purpose</u>

The purpose of endoscopic treatment with periureteral bulking agents in individuals with VUR 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 following PICO was used to select literature to inform this policy.

Populations
The relevant populations of interest are individuals with VUR who have either failed medical therapy and are eligible for surgery or have not failed medical therapy and may be ineligible for surgery. Primary VUR 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 VUR: 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 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 and bulking agents. Differences in morbidity are also important outcomes for both proposed uses. 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.

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A Cochrane review by Williams et al. (2019) included RCTs evaluating treatments for VUR. (18) Reviewers addressed a variety of interventions including long-term antibiotic prophylaxis, open surgery, and the use of bulking agents. The reviewers' decision to combine studies on open surgery and bulking agents limited the ability to analyze the efficacy of bulking agents. This Cochrane review selected 34 trials (N=4001 children). Four studies compared endoscopic injection with antibiotics alone and 3 studies assessed the outcome of febrile UTI. There was little or no difference in the risk of febrile UTI with endoscopic injection as compared to antibiotic therapy (relative risk [RR], 0.74; 95% CI, 0.31 to 1.78; low certainty evidence). Four studies comparing 2 different materials for endoscopic injection (n=425 children) reported VUR resolution rates and the 2 studies that compared Macroplastique to Deflux found Macroplastique to be probably superior to Deflux (3 months: RR, 0.50; 95% CI, 0.33 to 0.78; 12 months: RR, 0.54; 95% CI, 0.35 to 0.83; low certainty evidence).

In a systematic review and network meta-analysis, Mina-Riascos et al. (2021) evaluated the effectiveness and safety of endoscopic management versus ureteral reimplantation in pediatric patients (1 month to 15 years of age) with primary high-grade VUR. (19) The authors evaluated clinical experiments, quasi-experiments, and cohort studies for this review; bulking agents used in the studies included polytetrafluoroethylene, hyaluronic acid, collagen, dextranomer/ hyaluronic acid (Dx/HA), and polyacrylate-polyalcohol copolymer. Overall, 9 studies met the inclusion criteria - 7 observational and 2 clinical experiments. The primary outcome was the occurrence of post-treatment UTI. When comparing endoscopic management (Dx/HA and polyacrylate-polyalcohol copolymer) to ureteral reimplantation, no significant differences were found in mixed comparisons. Only 3 studies assessed complications with no statistically significant differences observed. Limitations of this systematic review include a lack of stratification by grade and patient age. Only 3 studies reported UTI diagnostic criteria, which may potentially lead to information bias.

A systematic review by Routh et al. (2010) identified randomized trials and observational studies evaluating Dx/HA treatment for pediatric VUR. (20) 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 7303 ureters injected with Dx/HA, 5633 (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 1109 children with initial grade IV VUR.

Randomized Controlled Trials

Periureteral Bulking Agents vs Surgery

The first RCT comparing periureteral bulking agents to 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-IV to receive endoscopic treatment with Dx/HA (n=22) or UR (n=19). (21) 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 of 35 ureters (91.4%) in the Dx/HA group and 32 of 32 ureters (100%) 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 of 35 ureters (85.7%) 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.

Salih et al. (2021) randomly assigned 60 pediatric patients older than 1 year of age with primary VUR grades III and IV to endoscopic injection of Dx/HA (n=30) or extravesical ureteral reimplantation utilizing an open Lich-Gregoir technique (n=30). (22) Indications for the intervention included recurrent UTI, impairment of renal function due to reflux, persistence of reflux after continuous antibiotic prophylaxis, and renal scarring, with the majority of cases operated on for breakthrough infections. Endoscopic Dx/HA was performed in 45 refluxing ureters and open ureteral reimplantation was conducted in 48 refluxing ureters. The mean follow-up for all patients was 17.7 ± 7.1 months. Overall reflux resolution was 80% (36/45) of the ureters in the Dx/HA group after a single injection and 93.75% (45/48) of the ureters in the ureteral reimplantation group (p=.007). Endoscopic injection failed in 9 ureters; therefore, another Dx/HA injection was given with improvement in 4 cases. The failed 5 cases after the second injection underwent salvage ureteral reimplantation. The mean operative time was longer for the ureteral reimplantation group versus the endoscopic group (110.3 ± 18.9 minutes vs. 28.6 ± 7.4 minutes; p<.001) and the median hospital stay was significantly shorter in the endoscopic injection group (1 vs. 4 days; p<.001). Trial results supported a finding of an increased success rate with ureteral reimplantation in comparison to endoscopic injection of Dx/HA; however, the minimally invasive endoscopic injection was superior in terms of operative time and hospital stay.

Periureteral Bulking Agents vs Antibiotic Prophylaxis

Findings from the Swedish Reflux trial in children were published by Brandstrom et al. (2010). (23-26) This non-blinded multicenter study included 203 children (128 girls, 75 boys) between the ages of 1 and 2 years with grade II to 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 (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. Complications occurred in 6 (9%) of the 64 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 (91%) of the 203 patients. Voiding cystourethrography findings indicated that VUR had resolved in 9 (13%) of 68 patients in the prophylaxis group, 20 (38%) of 52 in the endoscopy group, and 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 was 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 compared to the prophylaxis ($p<0.001$) and 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 in the prophylaxis versus the endoscopic groups. Rates of febrile UTI recurrence during follow-up were dramatically higher in girls (42/128 [33%]) than 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 (e.g., kidney damage, 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 evaluate the effectiveness of this treatment.

Capozza and Caione (2002) reported on the results of a study of 61 children with VUR (grades II-IV) who were randomized to receive an endoscopic subureteral implantation (n=40) of Deflux or 12 months of antibiotic prophylaxis (n=21). (27) Entry criteria included grades II to 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 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 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.

Children with Duplicated Ureters

No controlled studies have been published that compare bulking agents to other treatments in children with duplicated ureters. However, several case series are available, and these uncontrolled studies suggest reasonable response rates without 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-V VUR. (28) The mean age of participants was 3 years (range, 1 month to 12 years). Complete duplicated ureters were unilateral in 100 patients (81%) and bilateral in the remaining 13. A total of 136 refluxing units were treated with endoscopic injections of Dx/HA. Three months after treatment, children were evaluated with 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 ureters (25.7%) after a second injection and in the remaining 8 ureters (5.9%) after a third injection. There was one 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. (29) 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. (30) 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 vesicoureteral reflux (VUR) and are eligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes randomized controlled trials (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 suggests that morbidity rates are similar or lower with bulking agents. The evidence is sufficient to determine that the technology results in an 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 RCTs, 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 that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Urological Association

In 2017, the American Urological Association reviewed and confirmed the validity of its 2010 published guidelines on the management of primary VUR in children. (31) The Association recommended 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 guidelines were based on a review of the evidence, but the authors acknowledged the lack of robust RCT data.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not reveal any relevant ongoing clinical trials as of June 12, 2025.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	52327
HCPCS Codes	L8603, L8604, L8606

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2025	Document updated with literature review. Coverage unchanged. No new references added.
10/15/2024	Reviewed. No changes.
02/01/2024	Document updated with literature review. Coverage unchanged. No new references added; some removed.
10/15/2022	Reviewed. No changes.
11/01/2021	Document updated with literature review. Coverage unchanged. The following references were added: 2, 3, 5, 10, 11, 14, 17-19, 22, and 31.
10/15/2020	Reviewed. No changes.
11/15/2019	Document updated with literature review. Coverage unchanged. No new references added.
10/15/2018	Reviewed. No changes.
12/15/2017	Document updated with literature review. Coverage unchanged.
11/01/2016	Reviewed. No changes.
05/01/2015	Document updated with literature review. Coverage unchanged.
11/15/2014	Reviewed. No changes.
03/01/2013	Document updated with literature review. Coverage unchanged.
05/01/2008	New Medical Policy. This policy is no longer scheduled for routine literature review and update.