Medical Policy

BlueCross BlueShield Kansas
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Title: Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux (VUR)

Related Policies:	▪ *Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence*

Professional / Institutional
Original Effective Date: September 14, 1994 / February 1, 2006
Latest Review Date: September 23, 2025
Current Effective Date: August 17, 2010

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Populations	Interventions	Comparators	Outcomes
Individuals: • With vesicoureteral reflux who have failed medical therapy and are eligible for surgery	Interventions of interest are: • Endoscopic treatment with periureteral bulking agents	Comparators of interest are: • Ureteral reimplantation surgery	Relevant outcomes include: • Symptoms • Morbid events • Treatment-related morbidity
Individuals: • With vesicoureteral reflux who have not failed medical therapy and may be ineligible for surgery	Interventions of interest are: • Endoscopic treatment with periureteral bulking agents	Comparators of interest are: • Antibiotic prophylaxis • Ureteral reimplantation surgery • Surveillance only	Relevant outcomes include: • Symptoms • Morbid events • Treatment-related morbidity

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 evidence review 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

Vesicoureteral reflux (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.[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 hydonephrosis, 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 (ie, 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. Vesicoureteral reflux 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.[6,7,3,] The decision to administer prophylactic antibiotic treatment includes consideration of potential adverse events of long-term antibiotic therapy, 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 the 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 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 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 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% to 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 (ie, Dx/HA, polyacrylate polyalcohol, poldimethylsiloxane, 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=.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 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.

POLICY

A. Periureteral bulking agents may be considered **medically necessary** as a treatment of vesicoureteral reflux grades II, III, or 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 individuals with nonfunctioning kidney(s), Hutch diverticuli, active voiding dysfunction, and ongoing urinary tract infection.

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.

RATIONALE

The evidence review was created using searches of the PubMed database. The most recent literature update was performed through June 17, 2025.

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 1 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. Randomized controlled trials 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 individuals 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 individuals 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 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 review.

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 an 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 individuals 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), reduction 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. 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.

Study Selection Criteria

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.

REVIEW OF EVIDENCE

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% confidence interval [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 copolymer treatment for pediatric VUR.[20,] 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 versus Surgery

The first RCT comparing periureteral bulking agents with ureteral reimplantation was published by Garcia-Aparicio et al (2013). The authors randomized 41 children older than 1 year of age with VUR grades I to IV to endoscopic treatment with Dx/HA (n=22) or ureteral reimplantation (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

ureteral reimplantation. 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=.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 ureteral reimplantation group were free of VUR (p=.48). One patient in the Dx/HA group and 2 patients in the ureteral reimplantation group experienced treatment complications. Two patients in the Dx/HA group and none in the ureteral reimplantation 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 versus Antibiotic Prophylaxis

Findings from the Swedish Reflux Trial in children were published by Brandstrom et al (2010).[23,24,25,26,] This nonblinded multicenter study included 203 children (128 girls, 75 boys) between the ages of 1 and 2 years with grade II, 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 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 than in the prophylaxis ($p<.001$) and the surveillance groups ($p=.003$). 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 ($p=.002$) or the endoscopic group ($p=.14$); rates did not differ significantly between the prophylaxis and 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.

Capozza and Caione (2002) reported on the results of 61 children with VUR (grades II to IV) who were randomized to an endoscopic subureteral implantation (n=40) of Deflux or 12 months of antibiotic prophylaxis (n=21).[27,] 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.

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 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, III, IV, or V VUR.[28,] 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). Vesicoureteral reflux 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.[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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Urological Association

In 2017, the American Urological Association reviewed and confirmed the validity of its 2010 published guideline on the management of primary vesicoureteral reflux (VUR) in children.[31,] The Association recommended that patients older than 1 year of age who have a febrile breakthrough urinary tract infection while receiving continuous antibiotic prophylaxis be considered for 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 its 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 the use of injectable bulking agents to treat VUR.

Ongoing and Unpublished Clinical Trials

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

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

REVISIONS	
08-17-2010	Updated Description section.
	In Policy Section: ▪ Liberalized policy Form: "Deflux® is medically necessary for the treatment of vesicoureteral reflux." 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: ▪ Added HCPCS Codes: L8603, L8604 ▪ Removed CPT Code: 51715
	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: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.
01-08-2016	Updated Description section.
	In Policy section: ▪ Added Policy Guidelines.
	Updated Rationale section.
	In Coding section:

REVISIONS	
	▪ Added bulleted CPT and HCPCS descriptions.
	Updated References section.
10-13-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.
10-01-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed statement, "These diagnoses are otherwise subject to medical policy as stated above." ▪ Removed ICD-9 codes.
	Updated References section.
02-25-2021	Updated Description section
	In Coding section: • Added ICD-10 diagnosis code N11.0
	Updated Rationale section.
	Updated References section.
12-06-2021	Updated Description section
	Updated Rationale section.
	Updated References section.
09-27-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed Coding Bullets o CPT code 52327 would apply to the use of any bulking agent, including Deflux, to treat VUR. o There is a specific HCPCS code for Deflux: L8604. o Bilateral treatment of VUR is typical; therefore, each of the above codes could be used twice. ▪ Removed ICD-10 code N13.9
	Updated References Section
10-02-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated References Section
10-22-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
09-23-2025	Updated Description Section
	Updated Rationale Section
	Updated References Section

REFERENCES

1. Cooper CS. Diagnosis and management of vesicoureteral reflux in children. Nat Rev Urol. Sep 2009; 6(9): 481-9. PMID 19668250
2. Sargent MA. What is the normal prevalence of vesicoureteral reflux?. Pediatr Radiol. Sep 2000; 30(9): 587-93. PMID 11009294

3. Edwards A, Peters CA. Managing vesicoureteral reflux in children: making sense of all the data. F1000Res. 2019; 8. PMID 30647916
4. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. BMJ. May 07 1994; 308(6938): 1193-6. PMID 8180534
5. Roberts KB, Roberts KB, Downs SM, et al. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. Sep 2011; 128(3): 595-610. PMID 21873693
6. Arant BS. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. J Urol. Nov 1992; 148(5 Pt 2): 1683-7. PMID 1433588
7. Tamminen-Möbius T, Brunier E, Ebel KD, et al. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. J Urol. Nov 1992; 148(5 Pt 2): 1662-6. PMID 1433584
8. Hayn MH, Smaldone MC, Ost MC, et al. Minimally invasive treatment of vesicoureteral reflux. Urol Clin North Am. Aug 2008; 35(3): 477-88, ix. PMID 18761201
9. McMillan ZM, Austin JC, Knudson MJ, et al. Bladder volume at onset of reflux on initial cystogram predicts spontaneous resolution. J Urol. Oct 2006; 176(4 Pt 2): 1838-41. PMID 16945667
10. Yap TL, Chen Y, Nah SA, et al. STING versus HIT technique of endoscopic treatment for vesicoureteral reflux: A systematic review and meta-analysis. J Pediatr Surg. Dec 2016; 51(12): 2015-2020. PMID 27773360
11. Starmer B, McAndrew F, Corbett H. A review of novel STING bulking agents. J Pediatr Urol. Oct 2019; 15(5): 484-490. PMID 31591047
12. Vandersteen DR, Routh JC, Kirsch AJ, et al. Postoperative ureteral obstruction after subureteral injection of dextranomer/hyaluronic Acid copolymer. J Urol. Oct 2006; 176(4 Pt 1): 1593-5. PMID 16952696
13. Elder JS, Peters CA, Arant BS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol. May 1997; 157(5): 1846-51. PMID 9112544
14. Friedmacher F, Puri P. Ureteral Obstruction After Endoscopic Treatment of Vesicoureteral Reflux: Does the Type of Injected Bulking Agent Matter?. Curr Urol Rep. Jul 09 2019; 20(9): 49. PMID 31289951
15. Puri P, Kutasy B, Colhoun E, et al. Single center experience with endoscopic subureteral dextranomer/hyaluronic acid injection as first line treatment in 1,551 children with intermediate and high grade vesicoureteral reflux. J Urol. Oct 2012; 188(4 Suppl): 1485-9. PMID 22906657
16. Dwyer ME, Husmann DA, Rathbun SR, et al. Febrile urinary tract infections after ureteroneocystostomy and subureteral injection of dextranomer/hyaluronic acid for vesicoureteral reflux--do choice of procedure and success matter?. J Urol. Jan 2013; 189(1): 275-82. PMID 23174239
17. Lightfoot M, Bilgutay AN, Tollin N, et al. Long-Term Clinical Outcomes and Parental Satisfaction After Dextranomer/Hyaluronic Acid (Dx/HA) Injection for Primary Vesicoureteral Reflux. Front Pediatr. 2019; 7: 392. PMID 31612121
18. Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. Feb 20 2019; 2(2): CD001532. PMID 30784039
19. Mina-Riascos SH, Fernández N, García-Perdomo HA. Effectiveness and risks of endoscopic management compared to vesicoureteral reimplantation in patients with high-grade

vesicoureteral reflux: systematic review and network meta-analysis. Eur J Pediatr. May 2021; 180(5): 1383-1391. PMID 33474581
20. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics. May 2010; 125(5): 1010-9. PMID 20368325
21. Garcia-Aparicio L, Rovira J, Blazquez-Gomez E, et al. Randomized clinical trial comparing endoscopic treatment with dextranomer hyaluronic acid copolymer and Cohen's ureteral reimplantation for vesicoureteral reflux: long-term results. J Pediatr Urol. Aug 2013; 9(4): 483-7. PMID 23602843
22. Salih EM, Eldamanhory H, Selmy GI, et al. Comparison of Subureteral Endoscopic Injection of Dextranomer/Hyaluronic Acid and Lich-Gregoir Ureteral Reimplantation in the Treatment of Pediatric Primary Vesicoureteral Reflux: A Prospective Randomized Study. J Laparoendosc Adv Surg Tech A. Jun 2021; 31(6): 719-723. PMID 33751917
23. Brandström P, Esbjörner E, Herthelius M, et al. The Swedish reflux trial in children: I. Study design and study population characteristics. J Urol. Jul 2010; 184(1): 274-9. PMID 20478580
24. Brandström P, Esbjörner E, Herthelius M, et al. The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol. Jul 2010; 184(1): 286-91. PMID 20488494
25. Brandström P, Nevéus T, Sixt R, et al. The Swedish reflux trial in children: IV. Renal damage. J Urol. Jul 2010; 184(1): 292-7. PMID 20494369
26. Holmdahl G, Brandström P, Läckgren G, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol. Jul 2010; 184(1): 280-5. PMID 20488469
27. Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. J Pediatr. Feb 2002; 140(2): 230-4. PMID 11865276
28. Hunziker M, Mohanan N, Puri P. Dextranomer/hyaluronic acid endoscopic injection is effective in the treatment of intermediate and high grade vesicoureteral reflux in patients with complete duplex systems. J Urol. May 2013; 189(5): 1876-81. PMID 23159268
29. Molitierno JA, Scherz HC, Kirsch AJ. Endoscopic injection of dextranomer hyaluronic acid copolymer for the treatment of vesicoureteral reflux in duplex ureters. J Pediatr Urol. Oct 2008; 4(5): 372-6. PMID 18790423
30. Läckgren G, Wåhlin N, Sköldenberg E, et al. Endoscopic treatment of vesicoureteral reflux with dextranomer/hyaluronic acid copolymer is effective in either double ureters or a small kidney. J Urol. Oct 2003; 170(4 Pt 2): 1551-5; discussion 1555. PMID 14501658
31. Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol. Sep 2010; 184(3): 1134-44. PMID 20650499

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Urology Liaison Committee meeting, August 24, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, November 3, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
3. Blue Cross and Blue Shield of Kansas Urology Liaison Committee, August 2010.