Prior Authorization Review Panel  
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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<td>Policy Name: Vesicoureteral Reflux Treatment by Endoscopic Injection of Bulking Agents</td>
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**Type of Submission – Check all that apply:**

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0534 Vesicoureteral Reflux Treatment by Endoscopic Injection of Bulking Agents**

Clinical content was last revised on 08/09/2018. No additional non-clinical updates were made by Corporate since the last PARP submission.

Name of Authorized Individual (Please type or print):

Dr. Bernard Lewin, M.D.

Signature of Authorized Individual:

[Signature]

Revised July 22, 2019
Vesicoureteral Reflux Treatment by Endoscopic Injection of Bulking Agents

Number: 0534

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers endoscopic injection of dextranomer/hyaluronic acid copolymer (Deflux), polydimethylsiloxane (Macroplastique), polytetrafluoroethylene (Teflon), or other bulking agents approved by the U.S. Food and Drug Administration (FDA) for vesicoureteral reflux (VUR) medically necessary for the treatment of members with primary or secondary VUR who have any of the following conditions when conservative treatments (e.g., prophylactic antibiotics and clean intermittent catheterization) have failed:

- Children who have had a previously unsuccessful ureteral re-implantation; or
- Children who have stopped taking their medication as a result of drug intolerance or parental non-compliance; or
- Children whose reflux is associated with a thick-walled neuropathic bladder; or
- Deterioration of renal parameters regardless of reflux severity; or
- Lower grades of reflux (grades I to III); or
- Persistent reflux in post-pubertal female members; or

http://www.aetna.com/cpb/medical/data/500_599/0534.html
Recurrent, poorly controlled febrile urinary tract infections.

Aetna considers endoscopic injections of bulking agents for VUR experimental and investigational for members who do not meet these criteria because it has insufficient evidence of effectiveness for persons who do not meet these criteria.

**Note:** Members whose condition does not improve after 3 treatment sessions are considered treatment failures and are not likely to respond to this therapy. If the member fails to respond within 3 treatment sessions, further treatments are not considered medically necessary.

Aetna considers endoscopic injections of the following experimental and investigational for the treatment of members with primary or secondary VUR because their effectiveness has not been established: (not an all-inclusive list)

- Autologous blood
- Calcium hydroxyapatite
- Chondrocytes
- Durasphere
- Fat
- Glutaraldehyde cross-linked bovine dermal collagen (Contigen, C.R. Bard, Inc., Murray Hill, NJ; Zyplast, Collagen Corporation, Palo Alto, CA)
- Myoblasts
- Polyacrylamide hydrogel (BULKAMID)
- Polyacrylate-polyalcohol copolymer (VANTRIS).

**Background**

Vesico-ureteral reflux (VUR) is predominantly a disorder of childhood and occurs when urine passes backwards from the bladder to the kidneys during micturition. It is caused by vesico-ureteral sphincter incompetence. Reflux can predispose patients to urinary tract infections and renal scarring.

Primary VUR is the consequence of a congenital abnormality of the uretero-vesical junction, in which a deficiency of the longitudinal muscle of the intra-vesical ureter leads to an insufficient valvular mechanism. Secondary VUR is due to bladder obstruction and its resultant increased pressures. Obstruction of the bladder can
be anatomical or functional. The most common anatomical cause of VUR is posterior urethral valves, which are found in approximately 50% of VUR-afflicted boys. On the other hand, anatomical obstructions in females are extremely rare. Functional causes of VUR are far more common in girls; they include neurogenic bladder, non-neurogenic bladder, and bladder instability or dysfunction. Urinary tract infections (bladder infections) and accompanying inflammation can contribute to the development of VUR by decreasing bladder compliance, increasing intra-vesical pressures, and by distorting and weakening the uretero-vesical junction. Approximately 40% of children with urinary tract infections experience VUR.

Persons who undergo this procedure in the hospital can usually be discharged within 24 hours. More than 1 day's hospitalization is usually not necessary.

According to the International Classification System of VUR, reflux is graded I to V on the basis of the appearance of contrast in the ureter and upper collecting duct system during voiding cystourethrography:

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<tr>
<th>Reflux Grade</th>
<th>Description</th>
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<tr>
<td>Grade I</td>
<td>Reflux into the non-dilated ureter</td>
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<tr>
<td>Grade II</td>
<td>Reflux into the renal pelvis, and calyces without dilation</td>
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<tr>
<td>Grade III</td>
<td>Mid to moderate dilation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices</td>
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<tr>
<td>Grade IV</td>
<td>Moderate ureteral tortuosity and dilation of the renal pelvis, and calyces</td>
</tr>
<tr>
<td>Grade V</td>
<td>Gross dilation of the ureter, renal pelvis, and calyces, loss of papillary impressions, and ureteral tortuosity</td>
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Because of the high rate of spontaneous resolution in patients with grade I to III VUR, surgical intervention in these patients is rarely indicated. For patients with grade IV and V reflux, surgical correction (e.g., open ureteral re-implantation or endoscopic subureteral injection of Teflon) is highly successful.

Endoscopic Teflon therapy for VUR entails injection of polytetrafluoroethylene (Teflon) paste into the submucosa at the refluxing ureteral orifice to bolster it, thus eliminating the problem. In most patients, endoscopic injection of Teflon is performed on an outpatient basis. Hospitalization may be necessary if patient experiences hematuria, acute urinary retention, or pelvic pain; 1 or 2 repeat injections may be needed if the initial injection fails to correct reflux. The long-term
safety of endoscopic Teflon injection has not been clearly established. In particular, the question of whether there is a significant risk of Teflon particle migration remains unanswered.

In a recent study comparing the long-term outcome of the endoscopic correction of VUR of various injected substances, Sugiyama and colleagues (2004) stated that autologous blood is unsuitable for clinical application because of its poor durability; and the overall success rate of endoscopic surgery with glutaraldehyde cross-linked bovine dermal collagen or hyaluronan/dextranomer co-polymer was insufficient compared with surgical re-implantation. Furthermore, Schlussel (2004) noted that glutaraldehyde cross-linked bovine dermal collagen and hyaluronan/dextranomer copolymer do not have the long-term follow-up of Teflon.

Elder et al (2007) examined the use of endoscopic injection with dextranomer/hyaluronic acid co-polymer (Dx/HA, Deflux) as a curative option and as an alternative to antibiotic prophylaxis. The nationally representative PharMetrics Integrated Medical and Pharmaceutical database was used to conduct this retrospective analysis. Patients less than 11 years of age who were continuously eligible and had an International Classification of Diseases (ICD-9-CM) code for VUR were identified. Resource utilization and outcome measures were evaluated over a 6-month pre- and 12-month post-index period. Patients diagnosed with neuropathic bladder, posterior urethral valves, bladder exstrophy, ureterocele, or duplication anomaly were excluded. Patients were matched 3:1, antibiotic prophylaxis to Dx/HA, by age, gender, urinary tract infections (UTIs) prior to index date, and diagnosing physician specialty. The primary outcome assessed was UTIs. Of the matched patients, 114 received a prescription for antibiotic prophylaxis and 38 underwent endoscopic injection with Dx/HA. The average number of UTIs per year was 0.28 in the antibiotic cohort and 0.08 in the Dx/HA cohort, respectively. The incidence rate ratio (IRR) of 4.826 (p = 0.029) revealed that the average number of UTIs was 383 % higher for patients receiving antibiotic prophylaxis compared with patients who underwent endoscopic injection. The retrospective nature of the analysis did not allow for treatment randomization. Due to the stringent classification of UTIs, rates of UTIs may be under-estimated in both cohorts. The authors concluded that treatment with endoscopic injection with Dx/HA resulted in significantly fewer UTIs compared with children receiving antibiotic prophylaxis, supporting a role for Dx/HA as a first-line treatment option for patients with VUR.
Aaronson (2005) noted that open surgery remains the gold standard for the treatment of VUR. For children with grade-I or grade-II reflux, in whom spontaneous resolution is likely, antibiotic is usually parents' treatment of choice. On the other hand, for children with grade-IV or grade-V reflux, in which the space available for the bulking agent is very limited, and in cases of duplex ureters, in which there is a prolongation of the upper moiety non-refluxing ureter towards the bladder neck, which limits access to the refluxing orifice, open surgery is the treatment of choice. For children with grade-III reflux, endoscopic treatment may be considered as a treatment option. The author also stated that endoscopic treatment should also be considered for children who have had a previously unsuccessful ureteral re-implantation; those whose reflux is associated with a thick-walled neuropathic bladder; those with mild reflux who develop symptomatic breakthrough infections because of antibiotic resistance; or children who have stopped taking their medication as a result of drug intolerance or parental non-compliance.

Aaronson's observations regarding the use of endoscopic treatment for VUR are in agreement with the findings of other investigators (Stehr et al, 2004; Sugiyama et al, 2004; and Heidenreich et al, 2004). Stehr et al (2004) stated that ureteral re-implantation is the operative treatment of choice in cases with high-grade VUR. Alternatively in cases with lower-grade VUR, injection of bulking agents under the refluxive orifice can be performed. Sugiyama et al (2004) reported that the cure rate of endoscopic surgery with bulking agents could be improved by excluding high-grade VUR from the indications for endoscopic surgery. Heidenreich et al (2004) stated that the current indications for the surgical correction of VUR depend on the presence or absence of renal scars. If no scars are present, primary ureteral re-implantation is only indicated in high-grade bilateral VUR, whereas in the presence of renal scars surgical correction is indicated in low/high grade reflux at a young age. Endoscopic subureteral injections are primarily reserved for low-grade VUR with a 1 session success rate of over 90 %. Endoscopic subureteral injections appear to be an alternative to long-term antibiotics in grade I-III VUR.

Bae and colleagues (2010) compared cure rates and complications of Deflux and polydimethylsiloxane (Macroplastique) in the treatment of VUR. A total of 29 boys and 42 girls (total of 115 ureters) with a mean age of 6 years who had undergone endoscopic subureteral transurethral injection for VUR were enrolled. A single subureteral injection of Macroplastique was performed in 31 ureters in 23 children (group I; grade II: n = 4; grade III: n = 12; grade IV: n = 9; grade V: n = 6), and a single subureteral injection of Deflux was performed in 84 ureters in 48 children.
Renal ultrasound was done 1 day after injection, and voiding cysto-urethrography (VCUG) was done at 3 months. Successful reflux correction was defined as absent or grade I reflux on follow-up VCUG. No significant difference in success rates was observed between group I and group II [80.6 % (25/31) versus 78.6 % (66/84), respectively, p > 0.05]. The following post-operative complications developed: ureteral obstruction in 2 ureters of group I and 3 ureters of group II, asymptomatic urinary tract infection in 3 patients of group I and 2 patients of group II, and bladder calcification by erosion or mucosal necrosis in 2 patients of group I. The authors concluded that despite differences in material properties, both Deflux and Macroplastique were safe for the treatment of children with VUR.

Aubert (2010) carried out a literature review on the use of Macroplastique in VUR. A PubMed review of the literature since 1996 resulted in the selection of 24 studies of sufficient level of evidence to assess the effectiveness and tolerance of Macroplastique in the VUR in adults and children. The overall success rates at 1 year, 2 years and 9-years follow-up were 86 to 93 %, 80 to 92 %, and 77 to 100 %, respectively, which confirms the maintenance of good results over time, notably in VUR grade III and above. The success rate was similar for primary and secondary VUR except for total duplicity. Predictive criteria of success were the surgeon's experience, the low grade of VUR, and the absence of previous injection. In comparison with other bulking agents, the higher viscosity and absence of shrinkage of the product increase its reliability. After more than 12 years of use, no serious complication has been reported in the literature, reflecting the good tolerance of Macroplastique on the long-term. The author concluded that published studies on the use of Macroplastique in VUR confirmed its effectiveness, around 85 % of success for all grades, in both children and adults. The interest of Macroplastique is linked to its higher viscosity promoting a better reliability and reproducibility of the technique and its non-resorbable nature providing a permanent result, especially valuable in high-grade VUR with anatomical anomaly of the vesicoureteral junction or in VUR secondary to permanent lower urinary tract dysfunction.

The American Urological Association's guideline on management of primary VUR in children (Peters et al, 2010) recommended that patients receiving continuous antibiotic anaphylaxis with a febrile break-through UTI be considered for open surgical ureteral re-implantation or endoscopic injection of bulking agents for intervention with curative intent.
Alizadeh et al (2013) examined the incidence and presentations of ureteral obstruction following peri-ureteral injection of polyacrylate polyalcohol copolymer (PPC) for the treatment of VUR. From January 2010 to December 2012, a total of 88 patients (28 males, and 60 females) with 128 renal refluxing units (RRU), 131 ureters and a mean age of 6.7 +/- 5.9 years (range of 4 months to 32 years) underwent endoscopic correction of their VUR, using PPC. Exclusion criteria were dysmorphic appearing distal ureter, extra-vesical position of the ureteral orifice, persistent urethral obstruction (e.g., after previous valve ablation) and severe bladder trabeculation, making ureteral orifice unidentifiable. Patients were followed-up by ultrasound 1 month after the injection and then every 3 months. Cystography was performed 3 months post-operation. Mean follow-up time was 13.1 +/- 6.8 months (range of 3 to 27 months). Two patterns of obstruction were observed: early, during the first 3 to 4 days post-operation, in 4 patients (4 ureters; 3 %) which was associated with transient hydro-uretero-nephrosis (HUN) in 2 patients (2 ureters; 1.5 %); and late-onset obstruction in 3 patients (4 ureters; 3 %), which appeared 3 months to 1 year after surgery. It manifested itself by urinary tract infection and uremia in 1 patient with bilateral obstruction but was asymptomatic in the other 2. Early obstruction was managed expectantly and resolved in 3 to 12 months; however, late-onset obstruction needed catheter placement or open ureteroneocystostomy. The authors concluded that patients who undergo endoscopic treatment for their VUR using PPC need long-term follow-up until the safety of this substance is confirmed.

Stredele and colleagues (2013) determined the long-term effect in children of endoscopic treatment VUR using different bulking agents. Status of VUR, recurrence of UTI, and recurrence of febrile UTI were evaluated as end-points. From 1993 to 2005, these investigators injected 229 refluxive ureters (VUR grade II to IV) in 135 children. Mean age of the children was 55.7 months. These researchers used collagen in 98 (years 1993 to 2000), polydimethylsiloxane in 32 (years 1999 to 2000), and dextranomer/hyaluronic acid copolymer (Dx/HA) in 99 ureters (years 2000 to 2005). Of the 135 children, 127 underwent a VCUG (radiologic or nuclid) 3 months after the first injection, and 88 children a second VCUG (nuclid) after 37 months (mean) post-operatively. Clinically, patients were monitored for non-febrile or febrile UTI. Data were collected and analyzed retrospectively by chart review. After first injection with collagen, polydimethylsiloxane and Dx/HA, 52 %, 55 % and 81.5 % of the children were without VUR, respectively. Repeated injections were successful in only 21 % (collagen) to 42 % (Dx/HA). Of the 88 with a second VCUG, 48.5 % of the initially
reflux-free children developed relapse VUR after collagen, 45.5% after polydimethylsiloxane and 21.5% after Dx/HA injection. Clinically, there was a significant difference in post-operative UTI occurrence in favor of the Dx/HA group. The authors concluded that clinically and radiologically, Dx/HA exhibited the best results, giving better protection against UTIs and a better VUR cure rate.

Moreover, there was still a risk of VUR recurrence in successfully treated children after 3 years of follow-up.

In a single-center, single-surgeon, prospective, off-label study, Cloutier and colleagues (2013) evaluated the success of endoscopic treatment for VUR using polyacrylamide hydrogel. All patients underwent endoscopic subureteral double hydrodistention implantation technique injection followed by renal ultrasound and VCUG at 3 months post-operatively to confirm the absence of de-novo hydronephrosis and correction of VUR (grade 0). A total of 40 patients (69 refluxing ureters) underwent polyacrylamide hydrogel injection. Median age at surgery was 50 months. Bilateral reflux was identified in 29 patients (73%); 9 patients had duplex systems, 2 with reflux into both moieties. Reflux was graded using the International Reflux Study in Children grading system, with grade I seen in 9 ureters, II in 17, III in 20, IV in 18 and V in 5. Mean volume injected was 1.1 ml.

Success rate for grade I to III VUR at 3 months after a single treatment was 87%, and the overall success rate for all grades was 81.2%. The authors concluded that off-label use of polyacrylamide hydrogel injection therapy for primarily low-grade VUR demonstrated that the technique and short-term success rates were comparable to the most popular bulking agent, dextranomer/hyaluronic acid. Moreover, they stated that these results suggested that further trials comparing polyacrylamide hydrogel and dextranomer/hyaluronic acid would be worthwhile. The main drawbacks of this study were its small patient (40 patients) size, short follow-up (3 months), and the lack of a control group.

Moore and Bolduc (2014) prospectively compared the effectiveness of polydimethylsiloxane and dextranomer/hyaluronic acid injection for treatment of VUR. A total of 275 patients with documented VUR (grade I to V) were prospectively enrolled in a comparative study between April 2005 and February 2011 to be randomly treated endoscopically with either polydimethylsiloxane (Macroplastique) or dextranomer/hyaluronic acid copolymer (Deflux); 202 were treated with polydimethylsiloxane and 197 with dextranomer/hyaluronic acid copolymer. Patients were followed with VCUG at 3 months and renal ultrasonography at 3 months and at 1 year. Median follow-up was 4.3 years. The
primary outcome was surgical success (resolution versus non-resolution), and secondary outcomes included occurrence of adverse events. Vesicoureteral reflux was fully corrected in 182 of 202 ureters (90%) treated with polydimethylsiloxane, compared to 159 of 197 (81%) treated with dextranomer/hyaluronic acid copolymer (p <0.05). Obstruction was found in 5 ureters. Uni-variate and multi-variate analyses did not allow identification of any characteristics that could explain the significant difference in the success rates except for the type of product used. The authors presented the largest known prospective evaluation comparing 2 bulking agents for the treatment of VUR. Endoscopic injection of polydimethylsiloxane resulted in a better success rate than dextranomer/hyaluronic acid copolymer. The rate of resolution obtained with the latter is lower than those previously published due to the inclusion of high-grade reflux.

An UpToDate review on “Management of vesicoureteral reflux” (Matto and Greenfield, 2015) states that “Subureteric transurethral injection (STING procedure), an ambulatory day procedure, involves injecting a copolymer substance, such as dextranomer/hyaluronic acid (DxHA or DEFLUX) or polydimethylsiloxane, beneath the mucosa of the ureterovesical junction through a cystoscope. This injection changes the angle and perhaps fixation of the intravesical ureter, thereby correcting reflux. The success rate for correcting VUR by STING in one or more procedures ranges from 75 to over 90%. The success rate for initial correction of VUR (by ureter) varies by the severity of reflux and anatomic variables …. The success rate of a second STING procedure after an initial failed injection is high, ranging from 70 to 90%. The STING also has been utilized as a salvage procedure correcting VUR in 65% of patients who failed a previous open surgical reimplantation”.

Dogan and colleagues (2015) investigated the parameters which may affect the outcomes of endoscopic injection and compared the effectiveness of 2 different bulking agents both composed of dextranomer-hyaluronic acid copolymer. The data of patients who underwent endoscopic VUR treatment between 2003 and 2012 were retrospectively reviewed. Patients with history of previous open anti-reflux surgery, more than 1 failed endoscopic treatment for reflux, VUR caused by posterior urethral valve, duplex system and overt spinal dysraphism were excluded. Surgical technique was the classical STING method; 1 of the 2 dextranomer-hyaluronic acid copolymer agents was used (Deflux in 109 and Dexell in 131 patients). Both agents were composed of similar amounts of hyaluronic acid gel (15 mg in Deflux versus 17 mg in Dexell) but different sized dextranomer
microspheres (80 to 250 μm in Deflux and 80 to 120 μm in Dexell). During the follow-up, ultrasonography was performed with 3-month interval, antibiotic prophylaxis was continued until the control VCUG was taken. Patient based success was defined as the disappearance of reflux on control VCUG performed 3 to 6 months after the operation. Data were available for 240 patients. Mean age and mean post-operative follow-up were 78 ± 41 months and 19 ± 18 months. The overall success rate was 73.2%. Gender, laterality, grade of VUR, presence of voiding dysfunction, renal scar and pre-operative break-through infection (BTI) were not found to affect the outcome, whereas age younger than 54 months and previous history of failed endoscopic injection were found to negatively affect the outcome both in uni-variate and multi-variate analysis. The post-operative UTI (5 febrile and 43 non-febrile) rate was 20%. Both uni-variate and multi-variate analysis showed that post-operative UTI was more common in patients with persisting reflux, with pre-operative BTI and in girls. Patient characteristics, treatment outcome and post-operative UTI rate were similar regarding the used bulking agent. No ureteral obstruction was experienced within the follow-up period. The success rate for 2nd injection was about 60%, which was significantly lower than for the patients who underwent 1st injection. These researchers could not find any affecting factor for this difference. Contrary to the literature, the success rates in this study were similar in different reflux grades. These investigators explained this finding that they valued the intra-operative orifice configuration more than the grade which can be accepted as a patient selection bias. The lower success rate in children younger than 54 months could be explained by unstabilized bladder dynamics and higher voiding pressures in this age group, who are still in the toilet-training phase. Despite successful endoscopic treatment, UTI might occur. Post-operative UTI was more common in patients with persisting reflux, pre-operative BTI and girls. The similar success rates of both bulking agents proved that dextranomer size does not affect the clinical outcome. The authors concluded that endoscopic treatment of VUR has satisfying outcomes in properly selected cases. Younger age (less than 54 months) and previous history of failed injection history were found to be related to unfavorable results. Post-operative UTI occurs more frequently in patients with persisting reflux, pre-operative BTI history and girls. The choice of one of the dextranomer-based substances did not affect the surgical outcome and post-operative UTI development.

Karakus et al (2016) compared dextranomer/hyaluronic acid (Dx/HA; Dexell) and polyacrylate-polyalcohol copolymer (PPC; Vantris) in terms of effectiveness,
injection techniques and complications with special emphasis on vesico-ureteral junction obstruction (VUJO). A total of 95 patients who underwent endoscopic VUR treatment between 2009 and 2015 were retrospectively reviewed. Patients were divided into 2 groups: (i) patients underwent endoscopic treatment with PPC (n = 50 patients, 70 renal refluxing units), and (ii) patients underwent endoscopic treatment with Dx/HA (n = 45 patients, 74 renal refluxing units). The overall resolution rates based on the number of renal refluxing units studied was 88.6% and 70.3% in group 1 and group 2, respectively. Resolution rates were significantly better in group 1 compared to group 2. Vesico-ureteral junction obstruction requiring ureteral re-implantation or stent insertion developed in 7 patients in group 1. No VUJO was observed in group 2; VUJO in group 1 was markedly higher than that in group 2. The authors concluded that endoscopic treatment of VUR with PPC provided better resolution rates but higher VUJO rates compared to Dx/HA.

Periureteral Injection Technique (PIT) for High-Grade Vesico-Ureteral Reflux:

Asgari and colleagues (2016) noted that despite the benefits of the minimally invasive endoscopic treatment for VUR, it has a major drawback which is low success rate in high-grade VUR. For overcoming this problem, these researchers introduced a new modified technique of endoscopic treatment called periureteral injection technique (PIT). In a pilot study, a total of 37 ureters in 19 boys and 14 girls were treated, including 3 bilateral cases. Of 37 units, 30 (81.1%) had grade IV and 7 (18.9%) had grade V primary VUR (18 right, 13 left and 3 bilateral units). Sub-ureteral injection of PPC was done at the 5-o’clock and 7-o’clock positions in which the direction of injecting needles were almost parallel. Pre- and post-operative evaluation included urinalysis, urinary tract ultrasonography, voiding VCUG, dimercaptosuccinic acid scan and urodynamic studies. The median age was 38 months (range of 8 to 125). At 6 months follow-up confirmed with VCUG, the VUR disappeared in 34 (91.8%) units and 3 units [2 (5.4%) grade II and 1 (2.7%) had grade III]) had down-graded VUR. Complications included early fever due to urinary tract infection in 1 children, transient dysuria in 2 patients and low back pain in 1 patient. The authors concluded that the success rate of PIT for treatment of high grade VUR is high. However, they stated that further studies with more patients and longer follow-up are needed to draw final conclusion.

Bulking Agents:
Blais and colleagues (2017) noted that VUR is one of the most common pathologies encountered in pediatric urology. Better understanding of the evolution of VUR and new endoscopic surgical techniques in the last decades have led to major changes in the management of this pathology. However, the treatment algorithm remains complex and is composed of a wide variety of options, from active surveillance to surgical treatment. The 3 most popular techniques described in the literature are: (i) the subureteral Teflon injection (STING), (ii) the hydrodistention technique (HIT), and (iii) the double hydrodistention technique (double-HIT). STING technique was the first to be described. The technique consists of the injection of bulking agent, regardless of the agent, into the detrusor muscle immediately beneath the ureteral orifice at the 6 o’clock position. With the HIT, the ureter is distended with irrigation fluid from the cystoscope and the injection is made within the ureteral orifice, beneath the mucosa. The double-HIT is similar, but 2 injections are carried out -- a 1st injection is performed more proximally, within the ureteral tunnel, and a 2nd injection more distally, just under the ureteral orifice. Cross-linked bovine collagen has been the subject of many trials, revealing inconsistent success rates and high relapse rates. The variable degree of ingrowth of native fibroblasts, the shrinkage of the bulking agent, and the reported immunological reactions after injection of collagen are reasons why cross-linked bovine collagen has been abandoned by most centers. Injection of autologous material is appealing, as they behave as free grafts with the absence of foreign materials. Blood, chondrocytes, fat, and myoblasts were studied. Fat and chondrocytes showed high rates of long-term VUR recurrence. On the other hand, blood has not been largely studied and the experimental use of myoblasts in pigs failed. Calcium hydroxyapatite, a synthetic agent with identical chemical composition to teeth and bone, was investigated in animals and humans. Only few studies are available in the literature and reported success rates are widely variable. The authors stated that further studies with larger cohorts and longer follow-up are needed. Two agents have been recently introduced for the endoscopic injection of VUR: (i) polyacrylate-polyalcohol copolymer (PPC, Vantris), and (ii) polyacrylamide hydrogel (PAHG, Bulkamid). A multi-center survey showed a success rate of 93.8% after a single injection of PPC. Patients were monitored with ultrasound and voiding cystourethrogram. Most renal refluxing units had higher-grade VUR (55.8% Grade III and 19.5% Grade IV) and most patients (60%) were followed for more than 2 years. Moreover, PPC and Dx/HA have been compared in many trials. Endoscopic injection of PPC resulted in higher success rates. However, concerns have been raised with PPC regarding a high rate of ureteral obstruction. Finally, only few published series are available on

http://www.aetna.com/cpb/medical/data/500_599/0534.html
PAHG. These researchers noted that the success rate with this bulking agent appeared promising, but more trials are needed prior to extensive use.

Polyacrylate-Polyalcohol Copolymer (Vantris):

Warchoł and associates (2017) noted that the endoscopic correction of VUR in children is a well-accepted therapy in many pediatric urology centers. Polyacrylate-polyalcohol copolymer (PPC; Vantris) is one of the tissue-augmenting substances used for endoscopic reflux therapy. These investigators evaluated the results with PPC in children with VUR. From 2012 to 2016, a total of 125 children (73 girls and 52 boys) aged 0.6 to 17.9 years (mean of 4.9 ± 3.58) were treated with PPC; VUR was unilateral in 64 and bilateral in 61 patients, comprising 197 RRUs grades: II in 72, III in 50, IV in 33 and V in 42. Of these, primary reflux was present in 132 RRUs and 65 were complex cases; VCUG was performed 3 months after procedure. Follow-up was completed in 89.6% of patients (112 children), and 89.8% of RRUs (177 out of 197). Reflux resolved in 86.4% of RRUs after single injection, in 99.4% after 2nd and in 100% after the 3rd. The only significant, but serious complication observed was late ureteral obstruction after PPC injection correcting high grade reflux, which required ureteral re-implantation. This complication was found in 9 out of 112 children (8%), and in 11 out of 177 RRUs (6.2%), 1.1 to 2.9 years (mean of 2 ± 0.7) after the PPC injection. The longest follow-up reached 4.5 years. The authors concluded that these findings showed that the PPC injection is an effective procedure for treating all grades of VUR with high success rate. However, because of the possibility of late ureteral obstruction, which requires uretero-neocystostomy, long-term follow-up is mandatory.

Durasphere:

Ozkuvanci and colleagues (2018) stated that Durasphere EXP (DEXP) is a compound of biocompatible and non-biodegradable particles of zirconium oxide covered with pyrolytic carbon. These researchers evaluated the durability of off-label use of DEXP in the treatment of primary VUR in children. Patients who underwent sub-ureteric injection of DEXP for the correction of primary VUR were retrospectively reviewed. Patients aged greater than 18 years as well as those who had grade-I or grade-VVUR, anatomic abnormalities (duplicated system, hutch diverticulum), neurogenic bladder or treatment refractory voiding dysfunction were excluded. Radiologic success was defined as the resolution of VUR at the 3rd month control. Success was radiographically evaluated at the end of the 1st year.
A total of 38 patients (9 boys, 29 girls; mean age of 6.3 ± 2.7 years) formed the study cohort; 46 RRUs received DEXP (grade II: 22; grade III: 18; grade IV: 6). Mean volume per ureteric orifice to obtain the mound was 0.70 ± 0.16 ml. First control VCUG was done after 3 months in all patients. After the first VCUG, 6 patients had VUR recurrence. Short-term radiologic success of DEXP was 84.2%. Rate of radiologic success at the end of the 1st year was 69.4% (25/32). Lower age (p : 0.006) and lower amount of injected material (p : 0.05) were associated with higher success rates at the end of 1 year. The authors concluded that this was the first study to ascertain the outcomes of DEXP for treatment of primary VUR in children. After 1 year of follow-up, DEXP had a 69.4% success rate. These preliminary findings need to be validated by well-designed studies.

Furthermore, an UpToDate review on “Management of vesicoureteral reflux” (Matto and Greenfield, 2018) does not mention Durasphere as a management tool.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>52327</td>
<td>Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material</td>
</tr>
<tr>
<td>51715</td>
<td>Endoscopic injection of implant material into the submucosal tissue of the urethra and/or bladder neck</td>
</tr>
<tr>
<td>74420</td>
<td>Urography, retrograde, with or without KUB</td>
</tr>
<tr>
<td>74450</td>
<td>Urethrocystography, retrograde, radiological supervision and interpretation</td>
</tr>
<tr>
<td>74455</td>
<td>Urethrocystography, voiding, radiological supervision and interpretation</td>
</tr>
<tr>
<td>78740</td>
<td>Ureteral reflux study (radiopharmaceutical voiding cystogram)</td>
</tr>
<tr>
<td>L8604</td>
<td>Injectable bulking agent, dextranomer / hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:
Injection, chondrocytes, fat or myoblasts - no specific code:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8606</td>
<td>Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies</td>
</tr>
<tr>
<td>Q3031</td>
<td>Collagen skin test</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N13.70</td>
<td>Vesicoureteral-reflux</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


46. Mattoo TK, Greenfield SP. Management of vesicoureteral reflux. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed March 2015.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0534 Vesicoureteral Reflux Treatment by Endoscopic Injection of Bulking Agents

There are no amendments for Medicaid.