MEDICAL POLICY

POLICY TITLE	PERIURETERAL BULKING AGENTS AS A TREATMENT OF VESICOURETERAL REFLUX
POLICY NUMBER	MP-1.109

Original Issue Date (Created):	**12/29/2006**
Most Recent Review Date (Revised):	**9/9/2019**
Effective Date:	**11/1/2019**

I. POLICY

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 would be otherwise indicated.

The use of bulking agents as a treatment of vesicoureteral reflux in all other clinical situations is considered **investigational,** as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

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

Cross-references:

MP-4.012 Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

MP-2.096 Electromyography (EMG) (Needle and Non-Needle) of the Anal or Urethral Sphincter

II. PRODUCT VARIATIONS

Top

This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual MP-7.01.102, Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux. The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

Top

Vesicoureteral Reflux

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.

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.

Diagnosis

In most cases, VUR is diagnosed during evaluation of UTIs. Approximately one third of children with UTIs are found to have VUR.[2] The average age for UTI onset is 2 to 3 years, corresponding to the age when toilet training occurs. There also appears to be a genetic predisposition to VUR, and siblings may also be examined.

The criterion standard for diagnosis is voiding cystourography, a procedure that involves catheterization of the bladder. The severity of reflux is described by a grade, typically with the International Reflux Study Group grading system, which grades severity from I (reflux partway up the ureter) to V (massive reflux of urine up the ureter with marked tortuosity and dilation of the ureter and calyces). Determination of VUR grade is not exact, however, due to factors such as bladder pressure, which may vary at the time of measurement. In general, more severe reflux is associated with higher rates of renal injury, and less severe reflux (i.e., grade I and II) is associated with higher rates of spontaneous resolution and treatment success. Other factors found to be associated with the likelihood of spontaneous resolution of VUR and/or renal injury include age, sex, laterality, presence of renal scars, presence of voiding dysfunction, and history of UTI.

Treatment

Treatment strategies for VUR include bladder training, antibiotic prophylaxis, and surgical modification of the ureter to correct the underlying reflux. VUR is likely to resolve

spontaneously over 1 to 5 years; lower grades of reflux (i.e., grades I and II) are associated with a higher probability of spontaneous resolution. The decision to administer prophylactic antibiotic treatment includes consideration of potential adverse events of long-term antibiotic treatment, which can include allergic reactions and development of treatment-resistant bacteria resulting in breakthrough UTIs.

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

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

Bulking Agents

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

A variety of bulking agents have been tested for biocompatibility and absence of migration. Some compounds used in clinical studies are collagen (Contigen® [Allergan, Coolock; note: this product is no longer commercially available], Zyderm®, Zyplast® [Collagen Corp.]), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique), calcium hydroxyapatite (Coaptite), dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA), and polyacrylamide hydrogel (Bulkamid® [Contura International A/S]).

Adverse Events

According to case series data, injection of periureteral bulking agents is associated with low morbidity rates. Temporary postoperative ureteral obstruction may occur in less than 0.7% of patients following injection of bulking agents; this can be treated with ureteral stenting until the problem resolves. In comparison, on average, a 2% (range, 0%-9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. A large series published by Puri et al (2012) retrospectively reported on 1551 children injected with Dx/HA for high-grade VUR. 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. The incidence of febrile UTI did not differ significantly between patients who had ureter reimplantation (8% [16/210 cases]) and those who had endoscopic injections of Dx/HA (4% [4/106 patients]) (p=0.24).

Regulatory Status

In 2001, Deflux® 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." Contraindications include patients with nonfunctioning kidney(s), active voiding dysfunction, and ongoing urinary tract infection. Duplicated ureters were initially considered a contraindication to Deflux treatment, but this was changed to a precaution in 2007.

Note: Polytetrafluoroethylene may migrate, causing serious adverse events; this agent is not FDA-approved. Coaptite® (Merz Aesthetics, Raleigh, NC), Macroplastique®, and Tegress™ (CR Bard, Murray Hill, NJ) are categorized by FDA as "Agent, Bulking, Injectable for Gastro-Urology Use." Tegress™ was voluntarily withdrawn from the market by CR Bard on January 2007.

FDA product code: LNM.

IV. RATIONALE

Top

Summary of Evidence

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

For individuals who have VUR who have not failed medical therapy and may be ineligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, and treatment-related morbidity. The 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 the effects of the technology on health outcomes.

V. DEFINITIONS

Top

N/A

VI. BENEFIT VARIATIONS

Top

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

Top

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely

responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Top

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes ®					
52327					

HCPCS Code	Description
L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies
L8606	Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies

ICD-10-CM Diagnosis Codes	Description
N13.70	Vesicoureteral-reflux, unspecified
N13.71	Vesicoureteral-reflux without reflux nephropathy
N13.721	Vesicoureteral-reflux with reflux nephropathy without hydroureter, unilateral
N13.722	Vesicoureteral-reflux with reflux nephropathy without hydroureter, bilateral
N13.731	Vesicoureteral-reflux with reflux nephropathy with hydroureter, unilateral
N13.732	Vesicoureteral-reflux with reflux nephropathy with hydroureter, bilateral

IX. REFERENCES

Top

1. *Cooper CS. Diagnosis and management of vesicoureteral reflux in children. Nat Rev Urol. Sep 2009;6(9):481489. PMID 19668250*
2. *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):1193-1196. PMID 8180534*
3. *Arant BS, Jr. 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):1683-1687. PMID 1433588*
4. *Tamminen-Mobius 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):1662-1666. PMID 1433584*
5. *Hayn MH, Smaldone MC, Ost MC, et al. Minimally invasive treatment of vesicoureteral reflux. Urol Clin North Am. Aug 2008;35(3):477-488, ix. PMID 18761201*
6. *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):1838-1841. PMID 16945667*
7. *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):1593-1595. PMID 16952696*
8. *Elder JS, Peters CA, Arant BS, Jr., et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol. May 1997;157(5):1846-1851. PMID 9112544*
9. *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. Aug 17 2012;188(4 Suppl):1485-1489. PMID 22906657*
10. *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):275-282. PMID 23174239*
11. *Nagler EV, Williams G, Hodson EM, et al. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. Jun 15 2011(6):CD001532. PMID 21678334*
12. *Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics. May 2010;125(5):1010-1019. PMID 20368325*

13. *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: longterm results. J Pediatr Urol. Aug 2013;9(4):483-487. PMID 23602843*
14. *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):230-234. PMID 11865276*
15. *Brandstrom P, Esbjorner E, Herthelius M, et al. The Swedish reflux trial in children: I. Study design and study population characteristics. J Urol. Jul 2010;184(1):274-279. PMID 20478580*
16. *Brandstrom P, Esbjorner E, Herthelius M, et al. The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol. Jul 2010;184(1):286-291. PMID 20488494*
17. *Brandstrom P, Neveus T, Sixt R, et al. The Swedish reflux trial in children: IV. Renal damage. J Urol. Jul 2010;184(1):292-297. PMID 20494369*
18. *Holmdahl G, Brandstrom P, Lackgren G, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol. Jul 2010;184(1):280-285. PMID 20488469*
19. *Oswald J, Riccabona M, Lusuardi L, et al. Prospective comparison and 1-year follow-up of a single endoscopic subureteral polydimethylsiloxane versus dextranomer/hyaluronic acid copolymer injection for treatment of vesicoureteral reflux in children. Urology. Nov 2002;60(5):894-897; discussion 898. PMID 12429323*
20. *Kim SO, Shin BS, Hwang IS, et al. Clinical efficacy and safety in children with vesicoureteral reflux of a single injection of two different bulking agents--polydimethylsiloxane (Macroplastique) or dextranomer/hyaluronic acid copolymer (Deflux): a short-term prospective comparative study. Urol Int. 2011;87(3):299-303. PMID 21934268*
21. *Moore K, Bolduc S. Prospective study of polydimethylsiloxane vs dextranomer/hyaluronic acid injection for treatment of vesicoureteral reflux. J Urol. Dec 2014;192(6):1794-1799. PMID 24928269*
22. *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):1876-1881. PMID 23159268*
23. *Molitierno JA, Jr., 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):372-376. PMID 18790423*
24. *Lackgren G, Wahlin N, Skoldenberg 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):1551-1555; discussion 1555. PMID 14501658*
25. *Tekgul S, Riedmiller H, Hoebeke P, et al. EAU guidelines on vesicoureteral reflux in children. Eur Urol. Sep 2012;62(3):534-542. PMID 22698573*

26. *Peters CA, Skoog SJ, Arant BS, Jr., et al. Summary of the AUA Guideline on management of primary vesicoureteral reflux in children. J Urol. Sep 2010;184(3):1134-1144. PMID 20650499*
27. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 7.01.102, Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux September 2019.*
28.

X. POLICY HISTORY

Top

MP-1.109	**CAC 1/31/06**
	CAC 1/30/07
	CAC 3/27/07 Discussion tabled until April meeting
	CAC 4/24/07
	CAC 5/27/08
	CAC 5/26/09 Consensus
	CAC 5/25/10 Consensus
	9/10 Adopted BCBSA Policy
	CAC 7/26/11 Consensus
	CAC 8/28/12 Consensus, no change to policy statements. References updated. Codes reviewed 8/21/12
	12-20-12 New codes added
	7/24/13 Admin coding review complete
	9/24/13 Consensus review. No change to policy statements. References updated. Changed FEP variation to reference the policy manual. Coding reviewed.
	CAC 11/25/14 Consensus review. Policy statements unchanged. References updated. Rationale added. No changes to the policy statements. Coding Reviewed 11/17/2014
	CAC 11/24/15 Consensus review. Policy statements unchanged. No new references added. Rationale updated. Coding reviewed.
	CAC 11/29/16 Consensus review. No change to policy statements. References and rationale reviewed. Variation reformatting. Coding Reviewed.
	12/5/17 Consensus review. No change to policy statements. References and rationale updated.
	10/9/18 Consensus. No change to policy statements. References updated. Rationale condensed.
	9/9/19 Consensus. No change to policy statements. References updated.

POLICY TITLE	PERIURETERAL BULKING AGENTS AS A TREATMENT OF VESICOURETERAL REFLUX
POLICY NUMBER	MP-1.109

Top