BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux

Policy #: 454
Latest Review Date: August 2024
Category: GI/GU

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Proprietary Information of Blue Cross and Blue Shield of Alabama
An Independent Licensee of the Blue Cross and Blue Shield Association

POLICY:

Blue Advantage will treat **periureteral bulking agents** as a **covered benefit** as a **treatment of vesicoureteral reflux grades II-IV** when medical therapy has failed and surgical intervention is otherwise indicated.

Blue Advantage will treat the use of **bulking agents as a treatment of vesicoureteral reflux in other** clinical situations **as non-covered** and as **investigational**.

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

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contracts and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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. 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.

Diagnosis

In most cases, VUR is diagnosed after a febrile UTI episode or abnormality seen on ultrasound imaging. Approximately one-third of children with UTIs are found to have VUR. 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 cystourography, 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, voiding cystourethrography should not be performed routinely after the first febrile UTI. Voiding cystourethrography is indicated if renal and bladder ultrasonography reveals hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances. The severity of reflux is described by a grade, typically with the International Reflux Study Group grading system, which grades severity from I (reflux partway up the ureter) to V (massive reflux of urine up the ureter with marked tortuosity and dilation of the ureter and calyces). Determination of VUR grade is not exact, however, due to factors such as bladder pressure, which may vary at the time of measurement. In general, more severe reflux is associated with higher rates of renal injury, and less severe reflux (i.e., Grade I and II) is associated with higher rates of spontaneous resolution and treatment success. Other factors that have been 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 urinary tract infection.

Treatment

Treatment strategies for VUR include bladder training, antibiotic prophylaxis, and surgical modification of the ureter to correct the underlying reflux. VUR is likely to resolve spontaneously over a period of one to five 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 the consideration of potential adverse effects of long-term antibiotic therapy, which can include allergic reactions and the 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 above 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. 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 five 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 over 20 years and has been suggested as an alternative to either antibiotic or surgical therapy. Bulking agents can be injected into tissue around the ureteral orifices to minimize reflux. The STING procedure (sub-ureteral trans-urethral 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 coapted 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 ($p<0.00001$). 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®, Zyplast® [use discontinued due to immune reaction concerns], polytetrafluoroethylene paste (Teflon) [use discontinued due to concerns regarding particle migration, polydimethylsiloxane (Macroplastique) [use discontinued due to concerns of malignant potential], calcium hydroxyapatite(Coaptite), dextranomer/hyaluronic acid copolymer (Deflux®, Dexell®, or Dx/HA), polyacrylamide hydrogel (Bulkamid® [Axonics]), and polyacrylate-polyalcohol copolymer (Vantris®).

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% to 9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. In 2019, Friedmacher and colleague 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. 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. 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). Lightfoot et al (2019) evaluated long-term outcomes after Dx/HA injection for primary VUR in 99 patients (median follow-up: 8.4 years). 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 occurrences of febrile UTIs.

KEY POINTS:

The most recent literature update was performed through June 12, 2024.

Summary of Evidence

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

For individuals who have VUR who have not failed medical therapy and may be ineligible for surgery who receive endoscopic treatment with periureteral bulking agents, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, and treatment-related morbidity. The RCTs, which had relatively small sample sizes in each arm, compared periureteral bulking agents with antibiotic prophylaxis and/or surveillance only and reported mixed findings. Additional, larger studies are needed before conclusions can be drawn about the efficacy of periureteral bulking agents as first-line treatment for patients with VUR. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Urological Association

In 2017, the American Urological Association reviewed and confirmed the validity of its 2010 published guideline on the management of primary vesicoureteral reflux (VUR) in children. 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 use of injectable bulking agents to treat VUR.

KEY WORDS:
Deflux, Vesicoureteral Reflux, Bulking Agents, VUR

APPROVED BY GOVERNING BODIES:
In 2001, Deflux® received premarket application (PMA) approval from the U.S. Food and Drug Administration (FDA) for the "treatment of children with vesicoureteral reflux (VUR) grades II-IV" and remains the only FDA-approved bulking agent for VUR. Contraindications include patients with nonfunctioning kidney(s), hutch diverticulum, ureterocele, 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.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT:

52327	Cystourethroscopy (including ureteral catheterization); with subuteric injection of implant material

HCPCS:

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 agents, synthetic implant, urinary tract 1-mL syringe, includes shipping and necessary supplies

REFERENCES:

1. Ashley R, Vandersteen D. Outcome analysis of mini-ureteroneocystostomy versus dextranomer/hyaluronic acid copolymer injection for unilateral vesicoureteral reflux. J Urol 2008; 180(4 suppl):1611-4.
2. Bele U, Bratus D. Dextranomer-Hyaluronic Acid and Polyacrylate-Polyalcohol Copolymer are Equally Efficient for Endoscopic Treatment of Vesicoureteral Reflux in Children. Urol J. Aug 18 2019; 16(4): 361-365.

3. 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.
4. Edwards A, Peters CA. Managing vesicoureteral reflux in children: making sense of all the data. F1000Res. 2019; 8.
5. 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. 1997 May; 157(5):1846-51.
6. 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.
7. 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.
8. 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.
9. IOM (Institute of Medicine). 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press.
10. 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.
11. 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.
12. Mina-Riascos SH, Fernandez N, Garcia-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.
13. Moore K, Bolduc S. Prospective Study of Polydimethylsiloxane vs Dextranomer/Hyaluronic Acid Injection for Treatment of Vesicoureteral Reflux. J Urol. Jun 10 2014.
14. Nagler EVT, Williams G, Hodson EM et al. Interventions for primary vesicoureteric reflux. Cocharane Database Syst Rev 2011; (6):CD001532.
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. Oct 2012;188(4 Suppl): 1485-9.
16. 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.
17. 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.
18. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. Br Med J May 07 1994; 308(6938):1193-6.
19. Starmer B, McAndrew F, Corbett H. A review of novel STING bulking agents. J Pediatr Urol. Oct 2019; 15(5): 484-490.
20. Tekgul S, Riedmiller H, Hoebeke P et al. EAU guidelines on vesicoureteral reflux in children. Eur Urol. 2012; 62(3):534-42.
21. Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. Feb 20 2019; 2(2):CD001532.
22. 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.

POLICY HISTORY:

Medical Policy Group, October 2010
Available for comment January 27 – March 14, 2011
Medical Policy Group, September 2012
Medical Policy Group, October 2013
Medical Policy Group, January 2014
Medical Policy Group, October 2014
Medical Policy Group, October 2015
Medical Policy Group, August 2017
Medical Policy Group, August 2018 **(4):** Updates to Description and Key Points. No change to policy statement.
Medical Policy Group, August 2019
Medical Policy Group, August 2020
Medical Policy Group, August 2021
Medical Policy Group, August 2022
Medical Policy Group, August 2023
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, August 2024
UM Committee, August 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.