Corporate Medical Policy

Vesicoureteral Reflux, Treatment with Periureteral Bulking Agents

File Name: vesicoureteral_reflux_treatment_with_periureteral_bulking_agents
Origination: 6/2007
Last Review: 11/2023

Description of Procedure or Service

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney, most commonly seen in children. Severe reflux may damage the kidney through mechanical or immunological mechanisms. VUR predisposes an individual to urinary tract infections 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 central management strategy of children with VUR has been the reduction of reflux and prevention of renal damage induced by urinary tract infection (UTI).

In most cases, VUR is diagnosed after a febrile UTI episode or abnormality seen on ultrasound imaging. About one third of children with UTIs are found to have VUR. The average age for the onset of UTI 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 which 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. 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. 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.

Treatment strategies include bladder training, antibiotic prophylaxis, and surgical modification of the ureters to correct the underlying reflux. VUR is likely to resolve spontaneously over a period of 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 effects 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 individuals 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 surgical transplantation of the ureters to a different site in the bladder. Success rates for open surgery are reported to be greater than 95% and nearly 100% for individuals 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.

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 (subureteral 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 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 ($p<0.00001$). 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 of the 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), and polyacrylamide hydrogel (Bulkamid® [Axonics]), and polyacrylate-polyalcohol copolymer (Vantris ® [Promedon]).

In 2001, Deflux® received pre-market 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 non-functioning 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.

Note: Polytetrafluoroethylene may migrate, causing serious adverse events; this agent is not FDA approved. Coaptite®, Macroplastique®, and Tegress® are categorized by the FDA as "Agent, Bulking, Injectable for Gastro-Urology Use." Tegress was voluntarily withdrawn from the market by CR Bard as of January 31, 2007.

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

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Vesicoureteral Reflux, Treatment with Periureteral Bulking Agents

Policy

BCBSNC will provide coverage for periureteral bulking agents as a treatment of vesicoureteral reflux when it is determined to be medically necessary and when medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Treatment of Vesicoureteral Reflux with Periureteral Bulking Agents is covered

Periureteral bulking agents may be considered medically necessary as a treatment of vesicoureteral reflux grades II–IV when medical therapy has failed and open surgical intervention is otherwise indicated.

When Treatment of Vesicoureteral Reflux with Periureteral Bulking Agents is not covered

The use of bulking agents as a treatment of vesicoureteral reflux in clinical situations other than listed above is considered investigational.

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

Policy Guidelines

The International Reflux Grading system classifies VUR into 5 grades, depending on the degree of retrograde filling and dilation of the renal collecting system. This system is based on the radiographic appearance of the renal pelvis and calyces on a voiding cystogram, as follows:

- Grade I: Urine backs up into the ureter only, and the renal pelvis appears healthy, with sharp calyces.
- Grade II: Urine backs up into the ureter, renal pelvis, and calyces. The renal pelvis appears healthy and has sharp calyces.
- Grade III: Urine backs up into the ureter and collecting system. The ureter and pelvis appear mildly dilated, and the calyces are mildly blunted.
- Grade IV: Urine backs up into the ureter and collecting system. The ureter and pelvis appear moderately dilated, and the calyces are moderately blunted.
- Grade V: Urine backs up into the ureter and collecting system. The pelvis severely dilates, the ureter appears tortuous, and the calyces are severely blunted.

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 randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, morbid

events and treatment-related morbidity. Overall, studies found 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 group, compared periureteral bulking agents to antibiotic prophylaxis and/or surveillance only and had 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *52327, L8604*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 2/15/07.

Specialty Matched Consultant Advisory Panel - 5/8/2007

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 4/17/07.

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 4/9/08.

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 12/11/08.

Specialty Matched Consultant Advisory Panel - 9/2009

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BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 10/8/10.

Specialty Matched Consultant Advisory Panel review 12/2010

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Specialty Matched Consultant Advisory Panel review 11/2012

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Specialty Matched Consultant Advisory Panel review 11/2013

Medical Director review 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 10/09/14

Specialty Matched Consultant Advisory Panel review 11/2014

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BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 8/10/2017

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Specialty Matched Consultant Advisory Panel review 11/2020

BCBSA Medical Policy Reference Manual [Electronic Version]. 7.01.102, 8/12/2021

Specialty Matched Consultant Advisory Panel review 11/2021

Specialty Matched Consultant Advisory Panel review 11/2022

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Roberts KB, Roberts KB, Downs SM, et al. Urinary tract infection: clinical practice guideline for thediagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics.Sep 2011; 128(3): 595-610. PMID 21873693

Arant BS. Medical management of mild and moderate vesicoureteral reflux: followup studies of infantsand young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. J Urol.Nov 1992; 148(5 Pt 2): 1683-7. PMID 1433588

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STARMER B, MCANDREW F, CORBETT H. A REVIEW OF NOVEL STING BULKING AGENTS. J PEDIATR UROL. OCT 2019;15(5): 484-490. PMID 31591047

Specialty Matched Consultant Advisory Panel 11/2023

Medical Director Review 11/2023

Policy Implementation/Update Information

6/4/07	Notification of new policy. Periureteral bulking agents may be considered medically necessary as a treatment of vesicoureteral reflux grades II–IV when open surgical intervention is otherwise indicated. The use of bulking agents as a treatment of vesicoureteral reflux in clinical situations other than those listed is considered investigational. The use of bulking agents is contraindicated in patients with non-functioning kidney(s), hutch diverticuli, duplicated ureters, active voiding dysfunction, and ongoing urinary tract infection. Notification given 6/4/07. Effective date 8/13/07. (pmo)
01/05/09	HCPCS code L8604 effective January 1, 2009 added to Billing/Coding section. (pmo)
9/28/09	Reference sources added. (pmo)
6/22/10	Policy Number(s) removed (amw)
1/18/11	Specialty Matched Consultant Advisory Panel review 12/2010. References updated. Policy Guidelines updated. (mco)
12/20/11	Specialty Matched Consultant Advisory Panel review 11/2011. References updated. No changes to Policy Statements. (mco)
1/15/13	Specialty Matched Consultant Advisory Panel review 11/2012. Description section updated. References updated. No changes to Policy Statements. (mco)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/2013. References updated. Removed "duplicate ureters" as a non-covered clinical indication for use of bulking agents. Medical Director review 11/2013. (mco)

12/9/14 Information added to Policy Guidelines regarding superiority of one agent over another. Reference added. Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to Policy statements. (sk)

12/30/15 Reference added. Specialty Matched Consultant Advisory Panel review 11/18/2015. HCPCS L8603 and L8606 removed from policy. Policy Guidelines updated. "When medical therapy has failed" added to When Covered statement. (sk)

1/27/17 Specialty Matched Consultant Advisory Panel review 11/30/2016. (sk)

9/15/17 Reference added. Description updated. Policy Guidelines updated. (sk)

12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. (sk)

12/14/18 Reference added. Specialty Matched Consultant Advisory Panel review 11/28/2018. (sk)

10/29/19 Reference added. (sk)

12/10/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. (sk)

5/4/21 Reference added. Description section updated. Specialty Matched Consultant Advisory Panel review 11/18/2020. (sk)

12/14/21 Reference added. Specialty Matched Consultant Advisory Panel review 11/17/2021. (sk)

6/13/23 Policy review. Specialty Matched Consultant Advisory Panel review 11/16/2022. (sk)

12/29/23 References added. Specialty Matched Consultant Advisory Panel review 11/2023. Medical Director review 11/2023. (rp)