BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 7.01.102 Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux

Effective Policy Date: January 1, 2022

Original Policy Date: December 2012

Related Policies:

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

Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux

Description

Most commonly seen in children, vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney. The primary management strategies have been prophylactic antibiotics to reduce urinary tract infections and, for higher grade disease, surgical correction of the underlying reflux. Injection of periureteral bulking agents is proposed as an alternative to surgical intervention.

OBJECTIVE

The objective of this evidence review is to determine whether endoscopic treatment with periureteral bulking agents improves the net health outcome in individuals who have vesicoureteral reflux and (a) have failed medical therapy and are eligible for surgery or (b) have not failed medical therapy and may be ineligible for surgery.

POLICY STATEMENT

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

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

POLICY GUIDELINES

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

In 2001, Deflux was approved by the U.S. Food and Drug Administration (FDA) through the premarket application process for the "treatment of children with vesicoureteral reflux (VUR) grades II-IV" and remains the only FDA-approved bulking agent for VUR.[11,] Contraindications include patients with nonfunctioning kidney(s), Hutch diverticulum, ureterocele, active voiding dysfunction, and ongoing UTI. Duplicated ureters were initially considered a contraindication to Deflux treatment, but this was changed to a precaution in 2007.

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

FDA product code: LNM.

RATIONALE

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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American Urological Association

In 2017, the American Urological Association reviewed and confirmed the validity of its 2010 published guideline on the management of primary VUR in children.[35.] The Association recommended that patients older than 1 year of age who have a febrile breakthrough urinary tract infection while receiving continuous antibiotic prophylaxis be considered for open surgery or endoscopic injection of bulking agents. Specific bulking agents mentioned were Deflux and Macroplastique. The guideline was based on a review of the evidence, but its authors acknowledged the lack of robust randomized controlled trial data.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force has not addressed the use of injectable bulking agents to treat VUR.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Cooper CS. Diagnosis and management of vesicoureteral reflux in children. Nat Rev Urol. Sep 2009; 6(9): 481-9. PMID 19668250
2. Sargent MA. What is the normal prevalence of vesicoureteral reflux?. Pediatr Radiol. Sep 2000; 30(9): 587-93. PMID 11009294
3. Edwards A, Peters CA. Managing vesicoureteral reflux in children: making sense of all the data. F1000Res. 2019; 8. PMID 30647916
4. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. BMJ. May 07 1994; 308(6938): 1193-6. PMID 8180534
5. Roberts KB, Roberts KB, Downs SM, et al. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. Sep 2011; 128(3): 595-610. PMID 21873693
6. Arant BS. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. J Urol. Nov 1992; 148(5 Pt 2): 1683-7. PMID 1433588
7. Tamminen-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): 1662-6. PMID 1433584
8. Hayn MH, Smaldone MC, Ost MC, et al. Minimally invasive treatment of vesicoureteral reflux. Urol Clin North Am. Aug 2008; 35(3): 477-88, ix. PMID 18761201
9. McMillan ZM, Austin JC, Knudson MJ, et al. Bladder volume at onset of reflux on initial cystogram predicts spontaneous resolution. J Urol. Oct 2006; 176(4 Pt 2): 1838-41. PMID 16945667
10. Yap TL, Chen Y, Nah SA, et al. STING versus HIT technique of endoscopic treatment for vesicoureteral reflux: A systematic review and meta-analysis. J Pediatr Surg. Dec 2016; 51(12): 2015-2020. PMID 27773360
11. Starmer B, McAndrew F, Corbett H. A review of novel STING bulking agents. J Pediatr Urol. Oct 2019; 15(5): 484-490. PMID 31591047
12. Vandersteen DR, Routh JC, Kirsch AJ, et al. Postoperative ureteral obstruction after subureteral injection of dextranomer/hyaluronic Acid copolymer. J Urol. Oct 2006; 176(4 Pt 1): 1593-5. PMID 16952696
13. Elder JS, Peters CA, Arant BS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol. May 1997; 157(5): 1846-51. PMID 9112544
14. Friedmacher F, Puri P. Ureteral Obstruction After Endoscopic Treatment of Vesicoureteral Reflux: Does the Type of Injected Bulking Agent Matter?. Curr Urol Rep. Jul 09 2019; 20(9): 49. PMID 31289951
15. Puri P, Kutasy B, Colhoun E, et al. Single center experience with endoscopic subureteral dextranomer/hyaluronic acid injection as first line treatment in 1,551 children with intermediate and high grade vesicoureteral reflux. J Urol. Oct 2012; 188(4 Suppl): 1485-9. PMID 22906657
16. Dwyer ME, Husmann DA, Rathbun SR, et al. Febrile urinary tract infections after ureteroneocystostomy and subureteral injection of dextranomer/hyaluronic acid for vesicoureteral reflux--do choice of procedure and success matter?. J Urol. Jan 2013; 189(1): 275-82. PMID 23174239
17. Lightfoot M, Bilgutay AN, Tollin N, et al. Long-Term Clinical Outcomes and Parental Satisfaction After Dextranomer/Hyaluronic Acid (Dx/HA) Injection for Primary Vesicoureteral Reflux. Front Pediatr. 2019; 7: 392. PMID 31612121
18. Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. Feb 20 2019; 2: CD001532. PMID 30784039
19. 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. PMID 33474581
20. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics. May 2010; 125(5): 1010-9. PMID 20368325
21. Garcia-Aparicio L, Rovira J, Blazquez-Gomez E, et al. Randomized clinical trial comparing endoscopic treatment with dextranomer hyaluronic acid copolymer and Cohen's ureteral reimplantation for vesicoureteral reflux: long-term results. J Pediatr Urol. Aug 2013; 9(4): 483-7. PMID 23602843
22. Salih EM, Eldamanhory H, Selmy GI, et al. Comparison of Subureteral Endoscopic Injection of Dextranomer/Hyaluronic Acid and Lich-Gregoir Ureteral Reimplantation in the Treatment of Pediatric Primary Vesicoureteral Reflux: A Prospective Randomized Study. J Laparoendosc Adv Surg Tech A. Jun 2021; 31(6): 719-723. PMID 33751917
23. 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): 274-9. PMID 20478580
24. 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): 286-91. PMID 20488494
25. Brandstrom P, Neveus T, Sixt R, et al. The Swedish reflux trial in children: IV. Renal damage. J Urol. Jul 2010; 184(1): 292-7. PMID 20494369
26. Holmdahl G, Brandstrom P, Lackgren G, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol. Jul 2010; 184(1): 280-5. PMID 20488469
27. Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. J Pediatr. Feb 2002; 140(2): 230-4. PMID 11865276
28. 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): 894-7; discussion 898. PMID 12429323

29. Moore K, Bolduc S. Prospective study of polydimethylsiloxane vs dextranomer/hyaluronic acid injection for treatment of vesicoureteral reflux. J Urol. Dec 2014; 192(6): 1794-9. PMID 24928269
30. 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
31. 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. PMID 30318569
32. Hunziker M, Mohanan N, Puri P. Dextranomer/hyaluronic acid endoscopic injection is effective in the treatment of intermediate and high grade vesicoureteral reflux in patients with complete duplex systems. J Urol. May 2013; 189(5): 1876-81. PMID 23159268
33. Molitierno JA, Scherz HC, Kirsch AJ. Endoscopic injection of dextranomer hyaluronic acid copolymer for the treatment of vesicoureteral reflux in duplex ureters. J Pediatr Urol. Oct 2008; 4(5): 372-6. PMID 18790423
34. 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): 1551-5; discussion 1555. PMID 14501658
35. Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol. Sep 2010; 184(3): 1134-44. PMID 20650499

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2012	New policy	
March 2014	Replace policy	Policy updated with literature review, References 8-9, 17-19, and 23 added, other references renumbered. Policy statements unchanged.
March 2015	Replace policy	Policy updated with literature. Reference 17 added. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through June 22, 2017; no references added. Policy statements unchanged but "not medically necessary" corrected to "Investigational".
December 2018	Replace policy	Policy updated with literature review through June 7, 2018; no references added. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through May 31, 2019. no references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through June 29, 2020; references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through June 29, 2021; references added. Policy statements unchanged.