Medical Policy

BlueCross BlueShield of Kansas
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Title: Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux (VUR)

Professional
Original Effective Date: September 14, 1994
Revision Date(s): November 3, 2005; February 1, 2006; August 17, 2010; January 28, 2011; December 31, 2013
Current Effective Date: August 17, 2010

Institutional
Original Effective Date: February 1, 2006
Revision Date(s): September 16, 2010; January 28, 2011; December 31, 2013
Current Effective Date: September 16, 2010

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DESCRIPTION

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney and is most commonly seen in children. The primary management strategies have been use of 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.

Treatment of vesicoureteral reflux (VUR) is based on the assumption that 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 30-40 years. (1)

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 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 gold 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. (3, 4) 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. (1)

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 1–5 years; lower grades of reflux (i.e., grades I and II) are associated with a higher probability of spontaneous resolution. (3, 4) The decision to administer prophylactic antibiotic treatment includes the consideration of potential adverse effects 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. (5)

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. (6) 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.

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 either antibiotic or 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 of the compounds used in clinical studies are collagen (Contigen®, Zyderm®, Zyplast®), polytetrafluoroethylene paste (Teflon), polydimethylsiloxane (Macroplastique®), calcium hydroxyapatite (Coaptite®), and dextranomer/hyaluronic acid copolymer (Deflux® or Dx/HA).

Regulatory Status

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." 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®, 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.

POLICY

A. 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 is otherwise indicated.
B. The use of bulking agents as a treatment of vesicoureteral reflux in other clinical situations is considered **experimental / investigational**.

RATIONALE

Treatment of vesicoureteral reflux (VUR) with periurethral bulking agents is proposed as: 1) an alternative to other types of surgery for patients with high-grade VUR (predominantly grades IIII and IV) who have failed or are noncompliant with prophylactic antibiotics; and 2) an alternative to prophylactic antibiotics for patients with lower-grade or high-grade VUR. Appropriate outcomes for the comparison of bulking agents and other types of surgery are resolution of reflux and reduction in the rate of urinary tract infections (UTIs) and pyelonephritis. Since prophylactic antibiotic use

does not treat the underlying reflux, reduction in the rate of UTIs and pyelonephritis are reasonable outcomes for studies comparing antibiotics and bulking agents. Differences in morbidity are also important outcomes for both proposed uses.

An initial literature search was performed in 2005. The policy was updated regularly with a literature review using MEDLINE; most recently, the literature was searched from August 2012 through August 28, 2013. Following is a summary of key literature to date on use of periureteral bulking agents to treat VUR.

Efficacy of Bulking Agents for VUR

Systematic reviews:

The Cochrane Library conducted a review of randomized controlled trials (RCTs) on treatments for VUR. (7) The Cochrane review addressed a variety of interventions including long-term antibiotic prophylaxis, open surgery, and use of bulking agents and had limited ability to evaluate the efficacy of bulking agents because it combined studies on open surgery and bulking agents in the analysis. The review, however, is useful for examining the assumption that VUR increases the risk of complications. The Cochrane review, last updated in 2011, included 20 trials with a total of 2,324 children. No statistically significant differences were found in the overall risk of UTI or renal parenchymal injury between groups treated with surgery or bulking agents plus antibiotics versus antibiotic prophylaxis alone at any time point between 1 and 24 months. For example, a pooled analysis of data from 5 trials that evaluated repeat positive urine culture by 1-2 years found a nonsignificant risk ratio (RR) of 0.89 (95% confidence interval [CI]: 0.55-1.44). In addition, a pooled analysis of 4 trials that evaluated the outcome of new renal parenchymal defects at 4-5 years after treatment calculated a pooled RR of 1.09 (95% CI: 0.79-1.49). One statistically significant finding was a reduction in febrile UTI by 5 years with surgery or bulking agent treatment compared to antibiotics alone; in a pooled analysis of 2 studies (449 children), RR: 0.43; 95% CI: 0.27-0.70. These findings challenge the assumptions underlying the treatment of VUR, since one would expect a reduction in UTI if the hypothesis is correct that VUR is a modifiable risk factor for UTI and renal parenchymal damage.

A systematic review published in 2010 identified randomized trials and observational studies evaluating dextranomer/hyaluronic acid (Dx/HA) treatment for pediatric VUR. (8) A total of 47 studies, mainly retrospective case series, met eligibility criteria. A key inclusion was that studies report the postoperative success rate after a single injection of Dx/HA. Success was defined as resolution of VUR and could also include downgrading to grade 1 VUR. Of 7,303 ureters injected with Dx/HA, 5,633 (77%) were considered treatment successes. There were higher rates of success in children with lower-grade reflux compared to those with high-grade reflux. For example, the 164 children whose preoperative VUR was grade 1 had an 89% success rate compared to a 59% success rate among the 1,109 children with initial grade IV VUR.

Randomized controlled trials:

RCTs comparing periureteral bulking agents to other types of surgery:

The first RCT comparing periureteral bulking agents to ureteral reimplantation (UR) was published in 2013. Garcia-Aparicio and colleagues in Spain randomized 41 children older than 1 year of age

with VUR grades I-IV to receive endoscopic treatment with Dx/HA (n=22) or UR (n=19). (9) Indications for surgery included recurrent UTIs, persistent VUR after 2 years of antibiotic prophylaxis, impairment of renal function or another type of impairment due to VUR. A total of 35 refluxing ureters were treated with bulking agents, and 32 refluxing ureters were treated with UR. One year after treatment, 32 of 35 ureters (91.4%) in the Dx/HA group and 32 of 32 ureters (100%) in the surgical reimplantation group were cured; the difference between groups was not statistically significant, p=0.23. Findings were similar at final follow-up. At 5 years, 30 of 35 ureters (85.7%) in the Dx/HA group and 100% in the UR group were free of VUR; p=0.48. One patient in the Dx/HA group and 2 patients in the UR group experienced complications associated with the treatment. Two patients in the Dx/HA group and none in the UR group experienced fevers posttreatment. Rates of complications and adverse events did not differ significantly between groups. The results of this trial support that there are no large differences between the two treatments, but the study was not powered to detect smaller differences in outcomes and was also likely too small to detect differences in complications and adverse events.

RCTs comparing periureteral bulking agents to antibiotic prophylaxis:

Capozza and Caione reported on the results of a study of 61 children with VUR (grades II to IV) who were randomly assigned to receive an endoscopic subureteral implantation (n=40) of Deflux or 12 months of antibiotic prophylaxis (n=21). (10) Entry criteria included grades II to IV reflux present for at least 6 months. The antibiotic therapy was not specified and presumably was variable. It was not reported whether patients had been receiving antibiotic therapy during the preceding 6 months and experienced breakthrough UTIs, were noncompliant, or showed no evidence of spontaneous resolution of VUR. Therefore it is unknown whether the Deflux treatment was primarily considered an alternative to medical therapy or to surgical therapy. In part, due to the small numbers in the antibiotic control group, the distribution of the different grades of VUR was different in the 2 groups. Outcomes included improvement in reflux grade and measures of renal function; incidence of UTIs was not reported. The only statistically significant outcome reported was the improvement in reflux grade at month 12, with 69% of those in the Deflux group reporting a reflux grade of I or less, compared to only 38% in the antibiotic group. However, these results are not surprising, since antibiotic therapy itself is not intended to improve reflux grade but simply to sterilize the urine while awaiting the spontaneous resolution of VUR. Therefore, the only conclusion is that Deflux results in a higher incidence of VUR resolution compared to spontaneous resolution.

Findings from the Swedish Reflux trial in children were published in 2010. (11-14) This nonblinded multicenter study included 203 children (128 girls and 75 boys) between the ages of 1 and 2 years with grade III to IV reflux. Participants were not required to have failed antibiotic prophylaxis; thus the trial evaluated injection of a bulking agent as an alternative to antibiotic therapy. Most of the participants (194, 96%) were identified after a symptomatic UTI. Recruitment was more difficult than expected, and enrollment was stopped after 6 years. Participants were randomly assigned to 1 of 3 groups: antibiotic prophylaxis (n=69), endoscopic treatment with Deflux (n=66), or surveillance only (n=68).

The study aimed to simulate clinical practice, i.e., prophylactic antibiotics were prescribed without monitoring compliance, rather than ensuring that study participants took a known dose of antibiotics. Primary study outcomes included VUR status, and rates of febrile UTI and kidney damage after 2 years. Sixty-four of 66 patients randomly assigned to endoscopy received

treatment. Fourteen of 19 patients with still dilating VUR after 1 injection received a second injection; 2 patients received a third injection. The investigators reported that complications occurred in 6 of the 64 (9%) individuals who received endoscopic treatment. Overall, 187 participants (92%) completed at least 6 of the 8 follow-up visits; analysis was intention to treat. Two-year cystourethrography was done in 185 of the 203 (91%) patients. Findings from voiding cystourethrography were that VUR had resolved in 9 of 68 (13%) patients in the prophylaxis group, 20 of 52 (38%) in the endoscopy group, and 10 of 65 (15%) in the surveillance group. The proportion of patients in the 3 groups whose VUR was downgraded to grade I or II was 18 of 68 (26%), 17 of 52 (33%) and 21 of 65 (32%), respectively. There was a significantly greater proportion of patients whose VUR had resolved or had been downgraded in the endoscopy group compared to the prophylaxis (p=0.0002) and surveillance groups (p=0.003), but no statistically significant differences were found between the prophylaxis and surveillance groups. Thirteen patients (20% of the 66 patients randomly assigned to endoscopy) whose VUR had initially resolved or been downgraded experienced recurrences and had stage III or IV VUR at 2 years.

Febrile UTI rates by treatment group in girls were 8 of 43 (19%), 10 of 43 (23%), and 24 of 42 (57%), respectively, in the prophylaxis, endoscopic, and surveillance groups. Rates were significantly higher in the surveillance group than either the prophylaxis group (p=0.002) or the endoscopic group (p=0.14); rates did not differ significantly in the prophylaxis versus the endoscopic groups. Rates of febrile UTI recurrence during follow-up were dramatically higher in girls (42 of 128, 33%) than boys (7 of 75, 9%). Rates of febrile UTIs in boys were 2 of 26 (8%) in the prophylaxis group, 4 of 23 (17%) in the endoscopic group, and 1 of 26 (4%) in the surveillance group; there were no statistically significant differences between groups. The rate of new renal damage did not differ significantly among groups.

After stratifying findings by gender, the sample sizes in reported analyses were relatively small. There may have been insufficient power to evaluate some of the outcomes of interest, e.g., kidney damage and febrile UTIs. Moreover, findings might not be applicable to children outside of the restricted age range included in the study and to those with lower-grade VUR. Larger studies with a more representative sample of children with VUR are needed to further evaluate the effectiveness of this treatment.

RCTs comparing different bulking agents:

Oswald and colleagues randomly assigned 72 children with VUR to receive either Deflux or Macroplastique in addition to antibiotic prophylaxis. (15) Entry criteria included grades II to IV reflux (International Reflux Study Group grading system). Since all patients continued to receive antibiotic therapy, presumably, the bulking procedure was primarily considered an alternative to surgical reimplantation of the ureter. However, the patient selection criteria do not indicate whether patients had failed prior antibiotic therapy or had unresolved VUR. Correction of underlying VUR was similar in the 2 groups.

Kim and colleagues randomized 85 children aged 2-15 years with VUR (grades II-V) to receive subureteral injections of Macroplastique (n=42) or Deflux (n=43). (16) Eligibility included breakthrough UTI in addition to persistent VUR; most patients had started immediately on antibiotic prophylaxis after diagnosis (exact number not reported). Seventy-three of 85 children (86%) were available for the 3-month follow-up. The cure rate, defined as no evidence of reflux, was 69% in the Macroplastique group and 55% in the Deflux group; the difference between groups was

statistically significant, $p<0.05$. This study did not include a group of patients who received a treatment other than periureteral injection of bulking agents.

Children With Duplicated Ureters

No controlled studies have been published that compare bulking agents to other treatments in children with duplicated ureters. However, several case series are available, and these uncontrolled studies suggest reasonable response rates and do not report high complication rates in this population of patients. The largest series to date was published in 2013 by Hunziker and colleagues in Ireland. (17) The study included 123 children with complete duplex systems who were treated with Dx/HA for grade II-V VUR. The mean age of participants was 3 years (range: 1 month to 12 years). Complete duplicated ureters were unilateral in 100 patients (81%) and bilateral in the remaining 13. A total of 136 refluxing units were treated with endoscopic injections of Dx/HA. Three months after treatment, children were evaluated with voiding cystourethrography and bladder ultrasound. The rate of VUR resolution after 1 injection was 68.4% (93 of 136 ureters). VUR resolved in an additional 35 ureters (25.7%) after a second injection and in the remaining 8 ureters (5.9%) after a third injection. There was only 1 complication associated with the endoscopic injections, which was a case of frank hematuria. No patients needed ureteral reimplantation, and there was no evidence on ultrasound of delayed vesicoureteral junction obstruction. Five patients (4%) developed febrile UTIs during follow-up.

Other smaller case series have also evaluated bulking agents as a treatment of VUR in patients with duplicated ureters. For example, Molitierno and colleagues included 52 children with duplex ureters who had VUR grade II-V. (18) Overall, VUR was cured in 44 of 52 patients (85%) after 1 or 2 treatments with Dx/HA. Moreover, Lackgren and colleagues evaluated 68 children with duplex ureters and VUR. (19) Forty-three children (63%) had a positive response to treatment, defined as having their reflux resolve to grade 0 or I. There were no complications associated with treatment. Seventeen (25%) children required open surgery.

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. (20) In comparison, an average 2% (range, 0% to 9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation. (21) A large series published in 2012 by Puri and colleagues retrospectively reported on 1,551 children injected with Dx/HA for high-grade VUR. (22) 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 urinary tract injections occurred in 69 (5%) of patients during follow-up; the median length of follow-up was 5.6 years. Dwyer and colleagues compared the rate of febrile UTIs in 2 cohorts of patients with VUR. (23) The incidence of febrile UTI did not differ significantly in patients who had ureter reimplantation (8%, 16 of 210 cases) and those who had endoscopic injections of Dx/HA (4%, 4 of 106 patients), $p=0.24$

Summary

Injection of periureteral bulking agents has been proposed as a treatment for vesicoureteral reflux (VUR). Findings of 1 small RCT published in 2013, as well as other nonrandomized studies, suggest similar rates of reflux resolution compared to ureteral reimplantation surgery. The body of evidence suggests that morbidity rates are similar or lower with bulking agents. Thus, the use of bulking agents to treat VUR as an alternative to other surgical methods is considered medically necessary.

There is insufficient evidence comparing periureteral bulking agents to antibiotic prophylaxis; the single published RCT included a selected population and had a relatively small sample size. 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.

Practice Guidelines and Position Statements

In 2012, The European Association of Urology (EAU) published a guideline on the diagnosis and treatment of VUR in children. (24) The EAU recommends continuous antibiotic prophylaxis as initial treatment for children diagnosed with VUR in the first year of life and for children age 1-5 years who present with high-grade VUR. For children age 1-5 with lower grade VUR and no symptoms, surveillance without antibiotic prophylaxis is considered to be a reasonable option. The document states that surgical correction is a treatment option for patients with persistent symptoms and that endoscopic injection of bulking materials can have satisfactory results in children with lower grades of VUR

In 2010, the American Urological Association published an updated guideline on management of primary VUR in children. (25) They recommend that patients older than 1 year who have a febrile breakthrough UTI while receiving continuous antibiotic prophylaxis be considered for either 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 the authors acknowledged the lack of robust randomized controlled trials.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

52327	Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material
L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies

DIAGNOSIS

These diagnoses are otherwise subject to medical policy as stated above

593.70 Vesicoureteral reflux unspecified or without reflux nephropathy
593.71 Vesicoureteral reflux with reflux nephropathy, unilateral
593.72 Vesicoureteral reflux with reflux nephropathy, bilateral
593.73 Vesicoureteral reflux with reflux nephropathy, NOS

ICD-10 Diagnosis *(Effective October 1, 2014)*

N13.71 Vesicoureteral-reflux without reflux nephropathy
N13.721 Vesicoureteral-reflux with reflux nephropathy without hydroureter, unilateral
N13.731 Vesicoureteral-reflux with reflux nephropathy with hydroureter, unilateral
N13.732 Vesicoureteral-reflux with reflux nephropathy with hydroureter, bilateral
N13.9 Obstructive and reflux uropathy, unspecified

REVISIONS

08-17-2010	Updated Description section.
	In Policy Section: ▪ Liberalized policy Form: "Deflux® is medically necessary for the treatment of vesicoureteral reflux." To: "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 is otherwise indicated. The use of bulking agents as a treatment of vesicoureteral reflux in other clinical situations is considered experimental / investigational."
	In Coding Section: ▪ Added HCPCS Codes: L8603, L8604 ▪ Removed CPT Code: 51715
	Added Rationale Section
	Updated References
01-28-2011	Updated Rationale Section.
	Updated Reference Section.
12-31-2013	Policy reviewed.
	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.

REFERENCES

1. Cooper CS. Diagnosis and management of vesicoureteral reflux in children. Nat Rev Urol 2009; 6(9):481-9.
2. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. Br Med J 1994; 308(6938):1193-6.

3. Arant BS. Medical management of mild moderate, vesicoureteral reflux follow up studies of infants young, children. A preliminary report of the Southwest Pediatric Nephrology Study Group. J Urol 1992; 148(5 pt 2):1683-7.
4. Tamminen-Mobius T, Brunier E, Ebel KD et al. Cessation of vesicoureteral reflux for years in infants children, allocated to medical treatment. The International Reflux Study in Children. J Urol 1992; 148(5 pt 2):1662-6.
5. Hayn MH, Smaldone MC, Ost MC et al. Minimally invasive treatment of vesicoureteral reflux. Urol Clin North Am 2008; 35(3):477-88.
6. McMillan ZM, Austin JC, Knudson MJ et al. Bladder volume at onset of reflux on initial cystogram predicts spontaneous resolution. J Urol 2006; 176(4 pt 2):1838-41.
7. Nagler EVT, Williams G, Hodson EM et al. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev 2011; (6):CD001532.
8. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics 2010; 125(5):1010-9.
9. 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 2013; 9(4):483-7.
10. Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. J Pediatr 2002; 140(2):230-4.
11. Brandstrom P, Esbjorner E, Herthelius M et al. The Swedish reflux trial in children: I. Study design and study population characteristics. J Urol 2010; 184(1):274-9.
12. Brandstrom P, Esbjorner E, Herthelius M et al. The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol 2010; 184(1):286-91.
13. Brandstrom P, Neveus T, Sixt R et al. The Swedish reflux trial in children: IV. Renal damage. J Urol 2010; 184(1):292-7.
14. Holmdahl G, Brandstrom P, Lackgren G et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol 2010; 184(1):280-5.
15. 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 2002; 60(5):894-8.
16. 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.
17. 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 2013; 189(5):1876-81.
18. 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 2008; 4(5):372-6.
19. 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 2003; 170(4 Pt 2):1551-5; discussion 55.
20. Vandersteen DR, Routh JC, Kirsch AJ et al. Postoperative ureteral obstruction after subureteral injection of dextranomer/hyaluronic acid copolymer. J Urol 2006; 176(4 pt 1):1593-5.

21. 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 1997; 157(5):1846-51.
22. 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 2012; 188(4 Suppl):1485-9.
23. 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 2013; 189(1):275-82.
24. Tekgul S, Riedmiller H, Hoebeke P et al. EAU Guidelines on Vesicoureteral Reflux in Children. Eur Urol 2012; 62(3):534-42.
25. Peters CA, Skoog SJ, Arant BS et al. Summary of the AUA guidelines on the management of primary vesicoureteral reflux in children. J Urol 2010; 184(3):1134-44.

Other References:

1. Blue Cross and Blue Shield of Kansas Urology Liaison Committee meeting, August 24, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, November 3, 2005 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-03-05).
3. Blue Cross and Blue Shield of Kansas Urology Liaison Committee, August 2010.