

Protocol

Periureteral Bulking Agents as a Treatment of Vesicoureteral Reflux

(701102)

Medical Benefit		Effective Date: 10/01/14	Next Review Date: 11/19
Preauthorization	No	Review Dates: 09/10, 09/11, 09/12, 09/13, 07/14, 07/15, 11/15, 11/16, 11/17, 11/18	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With vesicoureteral reflux who have failed medical therapy and are eligible for surgery 	Interventions of interest are: <ul style="list-style-type: none"> • Endoscopic treatment with periureteral bulking agents 	Comparators of interest are: <ul style="list-style-type: none"> • Ureteral reimplantation surgery 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With vesicoureteral reflux who have not failed medical therapy and may be ineligible for surgery 	Interventions of interest are: <ul style="list-style-type: none"> • Endoscopic treatment with periureteral bulking agents 	Comparators of interest are: <ul style="list-style-type: none"> • Antibiotic prophylaxis • Ureteral reimplantation surgery 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Treatment-related morbidity

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.

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 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 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.

POLICY

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 non-functioning kidney(s), Hutch diverticuli, active voiding dysfunction, and ongoing urinary tract infection.

Bilateral treatment of VUR is typical.

BACKGROUND

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.¹

Diagnosis

In most cases, VUR is diagnosed during the evaluation of UTIs. Approximately one-third of children with UTIs are found to have VUR.² The average age for UTI onset is two to three 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 cystourethrography, 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, the presence of renal scars, the presence of voiding dysfunction, and history of UTI.¹

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 one to five 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 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. Advances in surgical technique, including the use of a lower abdominal transverse incision, 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 not 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 (greater than 60% over five 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.

Bulking Agents

The use of bulking agents in the treatment of VUR has been reported for more than 20 years and 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 (Macropastique), 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.⁷ In comparison, on average, a 2% (range, 0%-9%) ureteral obstruction and reoperation rate has been reported following ureteral reimplantation.⁸ A large series published by Puri et al (2012) retrospectively reported on 1551 children injected with Dx/HA for high-grade VUR.⁹ The only reported procedure-related complication was hematuria lasting up to 12 hours in three 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 two cohorts of patients with VUR.¹⁰ 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 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.

RELATED PROTOCOL

Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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