Bulking Agents in the Treatment of Stress Urinary Incontinence: History, Outcomes, Patient Populations, and Reimbursement Profile

Lindsey A. Kerr, MD

Department of Urology, University of Utah, Salt Lake City, UT

Stress urinary incontinence (SUI) can be defined as involuntary loss of urine during a period of increased abdominal pressure and in the absence of detrusor activity. Bulking agents used in the urethra are one of the newer but established technologies for the treatment of SUI. An understanding of the demographics of SUI will help in the selection of patients for bulking agent therapy. Knowledge of available materials, including their positive and negative aspects, is also required. Autologous fat, silicone beads, collagen, carbon particles, and polytetrafluoroethylene paste have all demonstrated success to some degree, but none have met both criteria for success (remaining efficacious over time and maintaining a low side-effect profile). An implantable solution of ethylene vinyl alcohol suspended in dimethyl sulfoxide, currently in clinical testing and review, shows minimal foreign body reaction and is one option being investigated to address patient needs for improved bulking therapy.

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Key words: Stress urinary incontinence • Bulking agents • Patient selection

With a significant number of Americans experiencing urinary incontinence and more than 60% of those exhibiting some component of stress urinary incontinence (SUI), treatment has evolved, over time, in response to need. There are now newer technologies following the advent of updated treatment protocols, but no single treatment type is applicable to all patients, and there

is often greater benefit from combination therapy. Bulking agents used in the urethra are one of the relatively newer but established technologies. An understanding of the demographics of SUI (85% female, 56% younger than 65 years) helps shape discussions regarding patient selection for bulking agents. Likewise, knowledge of available materials, including their positive and negative aspects, as well as reimbursement issues, must be clearly understood in terms of patient selection and necessary testing.

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Demographics of SUI

Stress urinary incontinence can be defined as a brief involuntary loss of urine associated with an increase of abdominal pressure and in the absence of detrusor activity. Historically, patients have been divided into 2 groups: those with urethral hypermobility and those with intrinsic sphincteric deficiency (ISD). ISD, a term defined in 1992,[1] is used to describe damage to the urethral sphincteric mechanism, regardless of etiology. The urethra might be damaged owing to fixation (as in cases of spina bifida), prior surgery, or denervation or muscle damage during childbirth. We now know that ISD and hypermobility can exist concomitantly as well as alone. The number of patients with stress incontinence has been roughly estimated at 25 million, with approximately 10% to 15% suffering from ISD. We expect these figures to continue to change as our understanding of the process and diagnostic acumen improve.

Urinary incontinence exacts a high price, both financially and in terms of quality of life, and has a substantial impact on individual patients, health care organizations, insurers, and society as a whole. The Alliance for Aging Research, in conjunction with the National Association for Continence, noted in a report to Congress that incontinence was 1 of the top 4 disease entities that detrimentally affect quality of life for our nation's seniors. In the Agency for Health Care Policy and Research Guidelines Update of 1996, Dr. T.W. Hu of the University of California, Berkeley, reported his data on the economic impact of incontinence.[2] Studying the population over 64 years of age only, Dr. Hu reported that routine costs of the condition were $10.2 billion. The majority of those costs were attributable to purchase of disposable products, such as pads, briefs, and catheters, as well as laundry charges. Other costs included treatment for urinary tract infections ($4.2 billion), care for injuries (eg, falls) resulting from attempts to reach the bathroom ($58 million), and longer hospital stays and additional hospital admissions ($7.8 billion). Total annual direct costs reached a record $23.6 billion per year for the Medicare-aged population alone. Indirect costs, such as lost time from work for a patient or caregiver, added $4.2 billion to the bill, for a total of $27.8 billion.

Incontinence is also a valid predictor of heavy nursing home use. Nursing home costs are between $39,000 and $43,000 per year, two thirds of which is covered by Medicare and Medicaid, thus adding to the financial impact of incontinence.[3]

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Bulking Agents: History and Outcomes Data

Bulking agents have a long medical history in fields outside of urology. They have been used for gastroesophageal reflux, for scars and wrinkles, as well as for patients with glottic insufficiency.[4–6] A variety of compounds have been used, with varying degrees of success. When bulking agents are used in the urethra, the goal is coaptation of the urethra during the storage phase, and maintenance of that coaptation during periods of increased abdominal pressure. Materials are implanted via the periurethral route (alongside the urethra) or, as in most cases, transurethrally. Implantation has to be accomplished without disturbing the patient's natural ability to void. The success of any product can be defined as its efficacy over time while maintaining a low side-effect profile. The ideal material should be biocompatible, nonimmunologic, and hypoallergenic. It should retain its bulking characteristics for a prolonged interval and not biodegrade or migrate. Additionally, it should be easy to prepare and implant. Although safety is a main advantage of bulking agents, the most common complications are pain during injection and transient urinary retention

and voiding dysfunction after implantation.

Autologous fat, silicone beads, collagen, carbon particles, and polytetrafluoroethylene (Teflon®) paste have all demonstrated success to one degree or another. However, none have met both success criteria of effectiveness over time and limited side effects. Autologous fat is difficult to harvest and is reabsorbed from the injection site at an unacceptably high rate.[7] The rare complication of fat embolization, with death, has also been reported. Silicone beads have demonstrated efficacy in some hands, but a possible association with development of some types of collagen vascular disease, as reported by patients after breast implants, remains an unanswered concern. This, and the issue of the worrisome migration of silicone particles, has slowed testing and delayed submission for US Food and Drug Administration (FDA) approval.[8] In the 1970s, Berg[9] described the use of Teflon for correction of urinary incontinence. Although it has a long history of successful use by subureteric injection in the treatment of reflux in children,[10] Teflon has not been approved in the United States, again owing to concern for particle migration/embolization and induction of inflammatory reactions such as granuloma formation.[11] Glutaraldehyde cross-linked (GAX) collagen has stood the test of time for safety. However, reimplantation requirements for collagen, as for all currently available bulking agents, diminish long-term efficacy of this therapy. After implantation of GAX collagen, neovascularization, accompanied by recruitment of host fibroblasts, can be seen. These fibroblasts might in fact replace the collagen and be responsible, ultimately, for continued continence when the presence of collagen can no longer be demonstrated.[12]

Carbon-coated bead suspensions demonstrate continence rates similar to those with GAX collagen. However, no preinjection antigenic testing is required. The beads can be cumbersome to inject. The biogel that suspends the beads flows fairly easily through the injection needle without carrying the beads along at a steady rate. The beads then tend to clog the needle, and the remaining material in the syringe is rendered useless. Sterile abscess formation has been reported with carbon-coated beads, but this might be an issue with many injectables that remain in a solid phase.[13]

Newer formulations look promising but must withstand the test of time. Liquid compounds that are inert and have limited foreign body reactions, as well as gels that precipitate to create bulk upon interaction with tissue or interstitial fluid, are being tested. These include hyaluronic acid and dextranomer microspheres.[14] An implantable solution of ethylene vinyl alcohol suspended in dimethyl sulfoxide shows minimal foreign body reaction and looks favorable. Interestingly, this solution has been used successfully in the treatment of brain aneurysms by direct implantation into the aneurysm itself. A mild foreign body response is elicited, but to date no untoward side effects in the brain have been noted. In clinical testing, the same solution has exhibited promising results after implantation into the urethra.[14]

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Special Patient Populations: Collagen as a Case Study

Shortliffe and coworkers[15] first reported GAX collagen for intraurethral use in 1989. After FDA approval in 1993, it was widely used for urethral ISD. The patient profile suggested older women with leakage at abdominal pressures of less than 65 cm H_20. Originally, collagen was thought to be ineffective in patients with urethral hypermobility. Most initial data therefore excluded this group of patients. A skin test with non–cross-linked collagen was required to elicit any possible allergic reactions. Implantation was initially performed periurethrally, although over time the transurethral route was increasingly preferred by surgeons. Many studies have demonstrated that transurethral implantation also requires less material than the periurethral method. The procedure can be performed in the hospital with sedation or in the office setting, with a periurethral local block in combination with viscous lidocaine per urethra. Most patients void immediately after surgery. The few side effects observed include hematuria, urinary retention

(transient), urinary tract infections, and urgency/frequency. Indwelling catheter treatment is avoided because it disrupts the newly recreated mucosal seal as the collagen molds itself around the catheter. The ideal patient in the early studies was thought to be an elderly woman with a fixed, open urethra, who otherwise could not tolerate a more invasive open surgical procedure.

McGuire and Appell[16] reported on their observation of 98 women and 89 men at 1 year after surgery and 45 women and 33 men at 2 years after surgery. They concluded that collagen implants dramatically improved the ability of the urethra to resist abdominal pressure increases without changing the voiding pressure required to allow bladder emptying (Table 1). After implantation, male patients similarly demonstrated an increase in abdominal pressure required to cause leakage; however, the data for men were not supported in further reports. Overall, men had lower success rates and required more collagen to render them dry. Herschorn and coworkers[17] reported on 31 women and 10 men with a mean follow-up of 8 and 6 months, respectively (Table 2). A follow-up study was published by this group on 181 women, mean age 64 years and mean follow-up 21 months. In this study, patients with hypermobility were included. For those with ISD alone, the dry rate was 23%, improvement at 52%, and failure at 25%.[18] Cross and colleagues[19] reported on 139 women (median age, 72 years) with ISD, of whom 73% had grade 3 incontinence. Seventy-four percent and 20% were "substantially improved" and "improved," respectively, with a median follow-up of 18 months. Eleven percent required

Table 1
Outcome Data from a Study of Transurethral Collagen Injection for Urinary Incontinence

Authors	Patient Population	Results	Conclusions	Comments/Findings
McGuire and Appell, 1994[16]	98 women, 89 men over 1 y; 45 women, 33 men at 2-y follow-up	Over 1 y: *ISD women:* Base ALPP: 29 cm H_2O Last ALPP w/collagen: 66 cm H_2O *ISD men:* Base ALPP: 43 cm H_2O Last ALPP w/collagen: 70 cm H_2O At 2 y: *ISD women:* Base ALPP: 30 cm H_2O Last ALPP w/collagen: 90 cm H_2O *ISD men:* Base ALPP: 34 cm H_2O Last ALPP w/collagen: 101 cm H_2O	Collagen injection dramatically improves the ability of the urethra to resist abdominal pressure without changing voiding pressure required to induce voiding. Injectable materials should not be considered a minor treatment for minor incontinence, nor should they be considered competitive with other treatments, including pubovaginal slings. Injectables can be used in conjunction with slings or artificial sphincters.	Urethral leakage that results when abdominal pressure is elevated indicates dysfunction due to poor closure mechanism or urethral hypermobility. Surgery designed to restore and hold the urethra in normal position during high abdominal pressure does not often resolve leakage due to poor closure mechanism. Generally, leakage at very low abdominal pressures indicates poor proximal urethral sphincter function. Patients with improvement often did not want or need further therapy. Complete dryness is not always necessary for success.

ISD, intrinsic sphincteric deficiency; ALPP, abdominal leak point pressure.

Table 2
Outcome Data from a Study of Intraurethral Collagen Injection for Urinary Incontinence

Authors	Patient Population	Results	Conclusions	Comments/Findings
Herschorn et al, 1992[17]	31 women followed for 3–15 mo (mean 8 mo); 10 men followed for 3–11 mo (mean 6 mo) Median patient age: 58 y	Women: 48% dry 42% improved 10% no improvement Average volume used for dry/improved cases: 12.7 mL, 2 sessions Men: 20% dry 50% improved 30% no improvement Average volume used for dry/improved cases: 51.8 mL, 6 sessions	Intraurethral injection of collagen is a safe and benign procedure, offering greatest benefit to female patients.	Female mean leak point pressure increased from 31 cm H_2O to 85 cm H_2O, post-treatment. The transurethral technique was used for men. For the majority of women, the periurethral technique was used. Complications were minimal.

"booster" injections at more than 6 months. These findings substantiated the need for repeated collagen implantation to maintain continence in many patients. Cross and colleagues[19] generated Kaplan-Meier curves to examine the relationship between grade of incontinence and probability of remaining dry. There was an inverse correlation, although it was not found to be statistically significant. The mean volume of collagen required to render patients dry increased as the grade of incontinence increased.

Herschorn and colleagues[18] report that intraurethral collagen injection is shown to be a safe and well-tolerated procedure that works equally well in younger and older women. Pretreatment bladder instability seems to be an adverse factor, whereas hypermobility is not, because patients with all types of incontinence fared similarly. Long-term durability of a successful result has been demonstrated, and repeat injections might restore success.[18] Additional studies suggest that some, but not all, patients with hypermobility do well.

ISD and Hypermobility

Because bulking agents were originally considered to have greatest utility in patients with ISD, and subsequent reimbursement followed along those lines, it was some time before patients with hypermobility were studied in the United States in any detail. Herschorn and coworkers[17,18] in Toronto demonstrated that the patient with hypermobility could derive benefit. In fact, no significant difference in outcomes was seen in patients with or without hypermobility ($P = .2889$) in their studies. Interestingly, patients with hypermobility required less collagen for a successful outcome. Monga and colleagues[20] reported on 60 women with genuine stress incontinence and urethral excursion ("mobility") up to 25 mm. Objective cure rates (according to urodynamic assessment) were 61% at 3 months and 48% at 24 months. Subjective success rates were 86% and 68% at 3 months and 24 months, respectively. Another report on 40 patients,[21] 23% with ISD, revealed that the hypermobile group required a similar number of implant procedures and volume of collagen compared with their counterparts with ISD alone. A logical conclusion derived from these studies is that ISD can exist in the presence of hypermobility and that this alone should not be a criterion for exclusion from bulking therapy. Bladder instability seems to be a predictor of a poorer outcome with bulking therapy. Patients with bladder instability should be appropriately evaluated.[18,19] Not all studies support the conclusion of poorer clinical results with bulking therapy in patients with unstable bladders, but common sense would dictate careful attention during patient selection and good medical management of the instability, both pre- and perioperatively.[20]

Male Incontinence

Closer examination of men with ISD resulted in several observations.[22–25] Patients with severe incontinence were unlikely to enjoy significant success with bulking therapy. Bladder neck contractures and scarring were associated with poorer continence status postoperatively. Unfortunately, men suffering from ISD were likely to be either postsurgical or postirradiation patients in whom scarring was often present. An antegrade implant method via a suprapubic tract proved superior in terms of finding a tissue plane that could accommodate implantation of a bulking agent. Yet durability of the implant still remained an issue even with this alternative implant technique (Table 3).

Elderly Populations

Several reports have been dedicated to the appropriate application of bulking

Table 3
Outcome Data from Three Studies of Transurethral Collagen Injection for Male Urinary Incontinence

Authors	Patient Population	Results	Conclusions	Comments/Findings
Elsergany and Ghoniem, 1998[23]	35 men with ISD (mean age 69 y) followed for 3–22 mo (mean 18 mo)	20% dry 31% improved 49% no improvement Average volume used for dry/improved cases: 8.2 mL, 2 sessions	Transurethral collagen injection is a safe and reasonable option for men with ISD. History of pelvic irradiation, urethral stricture, or involuntary bladder contractions can jeopardize results.	Procedures were performed under local anesthesia with monitored anesthesia care. Abdominal leak point pressure increased significantly after injection, from 69 cm H_2O to 116 cm H_2O. Complications are low.
Cummings et al, 1996[24]	19 men with post-radical prostatectomy stress incontinence, followed for 3–15 mo (mean 10 mo)	21% dry 37% improved 42% no improvement Average volume used for dry/improved cases: 13.8 mL, 1.8 sessions	Collagen injection can be helpful for men with stress incontinence induced by radical prostatectomy. Tissue scarring and preoperative severity of leakage affect results.	
Aboseif et al, 1996[22]	88 men with ISD (mean age 68 y) followed for 6–12 mo (mean 10 mo)	48% dry 37% improved 15% no improvement Average volume used for dry/improved cases: 22.7 mL, 3.4 sessions	Transurethral collagen injection is effective and safe in carefully selected patients with ISD. Tissue scarring and preoperative severity of leakage affected outcomes. No significant morbidity is associated with collagen injection.	Collagen was injected slowly, under direct supervision, on both sides until coaptation was achieved. Treatment endpoint was cure or 5 injections. Most injections were performed under local anesthesia.

ISD, intrinsic sphincteric deficiency.

therapy for elderly women. The definition of "elderly" has been subject to varied interpretation throughout the medical literature. Studies, at times, have labeled the average 65-year-old woman as "elderly." Today, the term "elderly" is more appropriately applied to those age 75 years or older. In this group and for those older women with significant health issues, a minimally invasive procedure for incontinence certainly is very appealing. Faerber[26] reported successful outcomes for elderly women with type I stress incontinence. Winters and coworkers[27] studied patients with an average age of 73.2 years. One to four implant procedures were required for continence, and the average volume required was 14.6 mL. Elderly women were more likely to have recurrent incontinence. The interval between therapy and recurrence was shorter than for their younger counterparts. Counseling of all patients is recommended.

For older women with significant health issues, a minimally invasive procedure for incontinence certainly is very appealing.

Historical View of Medicare Reimbursement

Bulking therapy has a well-established reimbursement profile and a successful track record of payment history within federal and private pay insurer systems. Medicare reimbursement for bulking therapy is predicated upon demonstration of ISD and very low Valsalva leak point pressures (VLPP). Private insurance carriers have followed suit, awarding reimbursement across the country. Fortunately, at the onset of coverage for this therapy, criteria for ISD were not strictly defined, because diagnostic testing performed by urogynecologists and gynecologists tended to vary from that performed by urologists.

Initially, to be eligible for reimbursement for GAX collagen implant therapy, VLPP was required to be 60 cm H_2O or less. The reimbursement criterion was revised upward to 100 cm H_2O in 1996, on the basis of data showing that patients with higher leak point pressures also derived benefit. Because collagen could be implanted in the office setting in many instances, performance of the procedure in ambulatory surgical facilities, such as hospital outpatient clinics, came under closer scrutiny.

In an effort to drive procedures to lower-cost environments and reduce overall health care system costs, the Centers for Medicare and Medicaid Services (CMS), the administrative body for Medicare, created a Hospital Outpatient Prospective Payment System (HOPPS) for many procedures, and Ambulatory Payment Classifications (APCs) were defined. Similar to the Diagnostic Related Groups (DRGs), the APC scheme classified "seemingly" similar procedures together for reimbursement.

In fiscal year 2001, ISD treatment was placed in the APC group with urethral repairs, including repair of a urethral injury (CPT 53505) and excision and fulguration of the Skene's glands (CPT 53270). No other procedure requiring an implantable device or material fell within this APC group. This grouping generated a facility fee for the hospital but no reimbursement for

Table 4
Centers for Medicare and Medicaid Payment Services Payment Schedule for Procedures and Ambulatory Payment Classifications (APCs), 2004

HCPCS Code	Description	Physician's Payment in the Office Setting	Physician's Payment in the Hospital or ASC	Hospital Facility Payment Mechanism
51715	Endoscopic injection	$299.82	$200.50	APC 0167
95028	Allergy skin tests	$8.83	N/A	APC 0370
Q3031	Skin test kit	N/A	N/A	N/A
L8603	Implant syringe	$351.34	N/A	Bundled into APC 0167

Payments shown are national averages. HCPCS, Healthcare Common Procedure Coding System; ASC, ambulatory surgical center; N/A, not applicable.

the bulking implant itself, effectively rendering bulking therapy cost prohibitive for institutions and ambulatory care facilities, and thereby severely restricting patient access to this minimally invasive therapy. Not all physicians were comfortable performing bulking therapy in the office setting. For some office practices, nonavailability of the rigid cystoscopic equipment required for accurate intraurethral placement became a limiting factor. After public feedback at a CMS "Town Meeting," a Medicare decision was reversed, and collagen was granted a "pass-through" reimbursement plan, which allowed payment of a facility fee and additional payment for every syringe used in a procedure. The physicians continued to bill separately for their technical services, using CPT code 51715. This reimbursement plan remained in effect for 2 years, until CMS determined that sufficient billing history was established to calculate more adequate payment levels for the therapy (Table 4).

As of fiscal year 2004, the HOPPS regrouped bulking therapy with other genitourinary prosthetics in a category-based system. Fiscal year 2004 facility payment for outpatient hospital services, including the implant, now averages $1638, up from $1058 2 years earlier. In the office setting, reimbursement for bulking therapy continues under the Durable Medical Equipment Prosthetics, Orthotics and Supplies (DMEPOS) Schedule. There is no facility fee for in-office therapy, but each individual implant used in a procedure is covered separately. In an effort to move select procedures from the higher-cost hospital environment to the lower-cost office environment, CMS reimbursement of a physician's technical fee for bulking therapy is 50% higher for an in-office procedure than for a hospital outpatient procedure. Payment is adjusted slightly by geographic region. According to the DMEPOS fee schedule, reimbursement per syringe is, on average, $351. There is a small reimbursement for placement of the skin test by a qualified health care provider, but there is no charge to the patient or the physician for the skin test material itself. ■

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Main Points

- A significant number of Americans experience urinary incontinence, with more than 60% of those exhibiting some component of stress urinary incontinence.
- Urinary incontinence exacts a high price in financial terms, relative to quality of life, but no single treatment is applicable to all patients, and there is often substantial benefit in combination therapy.
- A variety of bulking agents have been used with varying degrees of success in terms of providing nonimmunologic, hypoallergenic biocompatibility and bulking characteristics for prolonged periods without biodegradation or migration.
- Bulking agents, in addition to having a favorable safety profile, should be easy to prepare and implant.
- Intraurethral collagen injection has been demonstrated to be a safe, well-tolerated procedure equally effective in young and older women, with relatively long-term durability.
- Intrinsic sphincteric deficiency in the presence of hypermobility should not be a criterion for exclusion from bulking therapy.
- Bulking therapy has a well-established reimbursement profile and successful track record of payment history within both federal and private pay insurer systems.

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