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REVIEW

Innovations in the management of urethral stricture disease: emerging and regenerative strategies

Nicola Fazaa,[1#] Kamil Malshy,[2#*] Yuval Shafran,[1] Ameer Nsair,[1] Etan Eigner,[1] Melissa Atallah,[1] Shadie Badaan,[1] Kirolos Meilika,[2] Ariel Zisman[1]

[1]Urology Department, Rambam Health Care Campus, Haifa, Israel

[2]Department of Urology, University of Rochester Medical Center, Rochester, NY, USA

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Urethral stricture disease remains a challenging clinical entity within contemporary urology, requiring interventions that achieve sustained urethral patency while preserving functional outcomes. Established modalities such as urethral dilation, endoscopic urethrotomy, and urethroplasty using autologous grafts provide effective treatment for many patients. However, they are constrained by morbidity, graft contraction, and suboptimal success in complex or recurrent strictures. These inherent limitations have stimulated growing investigation of therapeutic strategies. Among device-based innovations, drug-coated balloon dilation, exemplified by the Optilume™, combines mechanical expansion with localized antiproliferative drug delivery and represents a significant evolution in endoscopic management. Pharmacologic adjuncts such as intralesional corticosteroids, mitomycin C, and hyaluronidase are already in clinical use to extend stricture-free intervals. Some emerging biologic strategies, including platelet-rich plasma, mesenchymal stem cells, and experimental inhibition of tyrosine kinase or YAP/TAZ signaling, represent prospective avenues for targeted antifibrotic therapy that remain largely in early translational stages. Parallel advances in regenerative medicine offer the potential for anatomically and functionally restorative repair. Bioengineered urethral grafts and 3D bio-printed constructs are designed to recapitulate native tissue architecture and support host cellular integration, providing patient-specific solutions that obviate the morbidity of autologous harvest. Preclinical and early clinical studies are reviewed with particular attention to scaffold composition, bioink formulation, and strategies to enhance vascularization and long-term functionality. This review aims to present these emerging approaches within the broader framework of contemporary urethral reconstruction, highlighting ongoing clinical trials and delineating the scientific, regulatory, and manufacturing challenges that must be addressed to facilitate their translation into routine clinical practice.

Key Words: tissue engineering, urethral reconstruction, stem cell therapy, biomaterials, buccal mucosa graft alternatives, urology

Introduction

Urethral stricture disease (USD) is a common urological condition resulting from fibrotic narrowing of the urethra, leading to progressive voiding dysfunction.[1] The estimated prevalence of USD among men in industrialized nations is approximately 0.9%, with a marked male predominance.[1–3] Anatomically, the male urethra is divided into anterior and posterior segments, with the bulbar and penile portions of

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[#]These authors contributed equally to this work

*Corresponding Author: Kamil Malshy. Email: kamilmalshy@gmail.com

the anterior urethra most commonly affected. These account for over 75% of cases, while panurethral or multifocal strictures occur less frequently.[1–4]

Etiology is multifactorial, encompassing inflammatory, traumatic, and iatrogenic factors. Instrumentation and prolonged catheterization contribute to 30–40% of cases, idiopathic origins account for 30–35%, inflammatory processes for 13–15%, and trauma for 4–19%.[1,5] Infectious urethritis, particularly nongonococcal urethritis, remains relevant in resource-limited settings but has declined significantly in developed regions.[6] Diagnosis begins with clinical symptom assessment, followed by objective testing such as uroflowmetry and post-void residual measurement. Imaging with retrograde urethrography (RUG) or voiding cystourethrography (VCUG), along with cystoscopy, is then used to define the location, length, and severity of the stricture.[6,7]

Therapeutically, management includes both endoscopic and open surgical modalities. Urethral dilation and direct-vision internal urethrotomy (DVIU) are commonly employed for short (<2 cm) urethral strictures but demonstrate modest long-term durability, with recurrence rates approaching 70% after repeated procedures.[6,8] Urethral stents have largely been abandoned due to complications, including migration and encrustation.[6,8] Open urethroplasty remains the cornerstone of definitive management, achieving success rates exceeding 85% in appropriately selected patients.[6,8] Excision and primary anastomosis (EPA) yields outcomes approaching 90% for short bulbar strictures, while substitution urethroplasty using buccal mucosa grafts provides durable results in longer lesions with success rates of 85–87%.[9] In extensive or pan-urethral disease, pedicled flap urethroplasty achieves success rates of 75–80%, and posterior urethral reconstruction following pelvic fracture demonstrates success near 88%.[8–10] Perineal urethrostomy offers a definitive option for recurrent, pan-urethral, or complex disease, with reported success of approximately 95%, though it necessitates lifelong perineal voiding.[8] An overview of treatment strategies according to urethral segment is summarized in Figure 1.

While endoscopic dilation, direct vision internal urethrotomy, and excision or substitution urethroplasty form the foundation of contemporary urethral reconstruction, limitations such as donor-site morbidity, graft contraction, and variable long-term success underscore the need for alternative strategies. The ongoing evolution of urethral stricture disease management now extends beyond conventional surgery, with emerging device-based, pharmacologic, and regenerative technologies offering the potential to enhance efficacy, reduce recurrence, and promote true tissue regeneration. Definitions of success in urethral stricture management vary across studies, which makes comparison challenging. Some define success functionally, improvement in symptoms or urinary flow, while others rely on anatomic confirmation, such as cystoscopic passage of a predetermined caliber.[11] Several clinical trials also use the need forany repeat intervention as their primary outcome.[12,13] Because these measures differ, reported success rates should be interpreted in the context of the criteria each study uses.

For the purpose of this review, these innovative modalities are categorized into four principal

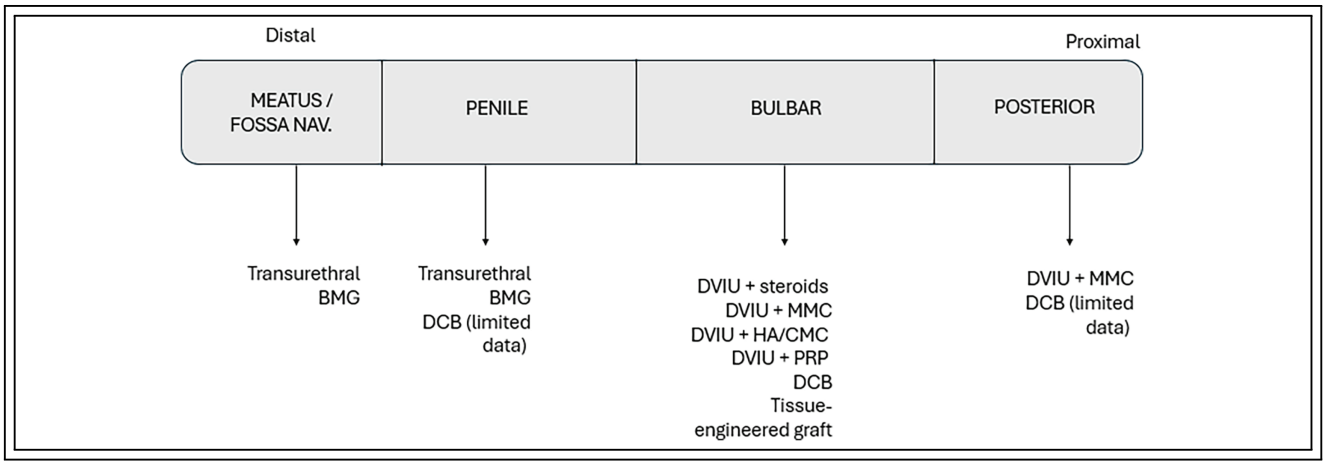

FIGURE 1. Overview of treatment options by urethral segment in urethral stricture disease (USD).
Abbreviations: DVIU, direct vision internal urethrotomy; BMG, buccal mucosal graft; DCB, drug-coated balloon; MMC, mitomycin C; HA, hyaluronic acid; CMC, carboxymethylcellulose; PRP, platelet-rich plasma.

domains: (A) therapeutic adjuncts to endoscopic treatment, aimed at reducing recurrence through pharmacologic or mechanical modulation of fibrosis; (B) endoscopic chemo-mechanical therapies, integrating controlled tissue ablation with localized drug delivery; (C) advanced trans-meatal or minimally invasive reconstructive techniques, improving surgical precision and functional outcomes; and (D) tissue-engineering and regenerative technologies, designed to restore native urethral architecture through biologically integrated repair. Yet, translating most of these innovations from concept to clinic requires rigorous validation. This review provides a comprehensive overview of the most recent literature on emerging treatments for urethral stricture disease.

Search Strategy

A narrative literature review was conducted using PubMed, Embase, and the Cochrane Library. The search included publications from January 2010 through November 2025, with selective inclusion of earlier landmark studies where relevant. Keywords and MeSH terms included "urethral stricture disease," "urethral fibrosis," "drug-coated balloon," "Optilume," "endoscopic adjuncts," "platelet-rich plasma," "mesenchymal stem cells," "tissue engineering," "bioengineered urethra," and "3D bioprinting." Reference lists of selected articles were manually reviewed to identify additional relevant studies. Both preclinical and clinical studies published in English were considered.

An AI-based image generation tool was used solely to create a schematic illustration for Figure 2. The tool was not used for text generation, data analysis, study design, or interpretation of results. All scientific content and conclusions were determined exclusively by the authors.

Therapeutic Adjuncts in Endoscopic Management

Historical adjuncts

Early attempts to improve the outcomes of endoscopic treatment for USD emphasized local delivery of antifibrotic and antiproliferative agents through intraurethral instillation or intralesional injection.

Intraurethral brachytherapy

Intraurethral brachytherapy was among the first explored, reported in 2001 in 17 patients with recurrent strictures treated by DVIU, followed by catheter-based delivery of iridium-192.[14] After 20 months, 94.1% (16/17) remained recurrence-free without major complications, though this experience has not been replicated and is generally abandoned in current practice and guidelines.[14]

ACE-inhibitors-captopril

ACE-Inhibitors-Captopril is an angiotensin-converting enzyme inhibitor with antifibroblastic activity, demonstrating inhibition of fibroblast proliferation in experimental ureteral injury models.[15,16] In a phase II study of 56 men, intraurethral instillation of 0.1% or 0.5% captopril gel following DVIU significantly reduced stricture recurrence compared with placebo, but this remains the only human trial to date.[17]

Botulinum toxin type A (BoNT-A)

By inducing temporary neuromuscular blockade and reducing local tensile forces, botulinum toxin type A (BoNT-A) has been investigated for its potential to mitigate scar contraction.[18] In a rat model, periurethral injection of BoNT-A (1.5 U) has shown significant superiority in fibrosis reduction when compared to saline injections.[19] A small clinical report of three patients with recurrent posterior strictures treated with BoNT-A (100 U) during repeat DVIU demonstrated maintained urethral patency in two patients at nine months and one at twelve months.[20] Although early findings were encouraging, the limited evidence precludes firm conclusions regarding safety or efficacy.

Contemporary pharmacologic adjuncts

Adjunctive pharmacologic therapy following DVIU has gained renewed interest as a means of prolonging urethral patency and reducing recurrence through modulation of fibrosis.[21]

Chemotherapeutic agents

Chemotherapeutic agents, particularly mitomycin C (MMC), represent the most extensively studied class. MMC suppresses fibroblast proliferation and collagen synthesis, key drivers of scar formation in urethral stricture disease.[21] A systematic review and meta-analyses demonstrated that adjunctive MMC use results in the lowest recurrence rates among all evaluated pharmacologic adjuncts.[22] While evidence of efficacy exists, caution is warranted; rare but severe complications such as osteitis pubis, urosymphyseal fistula, and rectourethral fistula have been reported in the treatment of bladder neck stenosis, particularly with injections performed at the 6 and

12 o'clock positions.[12] Appropriate dosing and injection technique are therefore critical to minimize risk. Additional mitotic inhibitors, including docetaxel and paclitaxel, have demonstrated antifibrotic potential through microtubule stabilization and inhibition of fibroblast migration, though clinical experience remains limited.[23]

Corticosteroids

Corticosteroids include triamcinolone and methylprednisolone, have been widely used due to their anti-inflammatory and antiproliferative properties. Delivered via intralesional injection or intraurethral instillation, these agents aim to mitigate scar remodeling following endoscopic incision. Multiple randomized trials and systematic reviews have shown that local steroid therapy following DVIU significantly prolongs the time to recurrence and may modestly reduce overall recurrence rates.[24] In the largest systematic review, which included seven randomized controlled trials and 365 patients, adjunctive local steroid administration after DVIU was associated with both a longer recurrence-free interval and a lower risk of stricture recurrence compared with DVIU alone.[24] Given their availability, safety profile, and low cost, corticosteroids remain a practical and evidence-supported adjunct to endoscopic management.

Hyaluronidase

Hyaluronidase is an enzymatic agent that hydrolyzes extracellular hyaluronic acid and glycosaminoglycans and has been explored as both monotherapy and part of multidrug regimens.[25] Clinical studies have reported encouraging outcomes with post-DVIU instillation of hyaluronic acid/carboxymethylcellulose (HA/CMC) mixtures, achieving success rates between 53% and 76% at one year.[26] In a multicenter randomized controlled trial involving 120 patients, adjunctive HA/CMC instillation following DVIU reduced stricture recurrence to 9.4% compared with 22.9% in the control group and was associated with significantly lower postoperative pain and higher patient satisfaction.[27] These findings support HA/CMC as a promising antifibrotic adjunct capable of extending recurrence-free intervals and improving postoperative recovery. Combination therapy using hyaluronidase with triamcinolone, MMC, and N-acetylcysteine achieved success rates up to 82% without significant complications.[28] These findings suggest a potential synergistic benefit, though further prospective trials are needed to define its role within multimodal adjunctive protocols.

Emerging biologic and molecular adjuncts

Biologic and cellular adjuncts

Recent therapeutic advances have shifted focus toward biologically driven and molecular approaches that directly target the mechanisms underlying urethral fibrosis. Platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs). Have gained particular attention for their capacity to enhance tissue regeneration and attenuate scar formation. PRP, a concentrated autologous platelet suspension rich in angiogenic and reparative mediators such as TGF-β, PDGF, and VEGF, promotes vascularization and organized collagen remodeling.[29] In a randomized controlled trial of 87 men with bulbar urethral stricture, submucosal PRP injection following DVIU significantly reduced recurrence rates compared with saline injection, 9.1% versus 26.8% at one year and 21.9% versus 43.9% at two years.[30] Similarly, adipose-derived MSCs have demonstrated antifibrotic potential through suppression of type I and III collagen deposition and downregulation of inflammatory cytokines, including TNF-α and IL-1β.[31] Experimental models have confirmed reduced expression of fibrosis-associated genes after MSC administration.[31,32]

A recent retrospective study involving 78 men with short bulbar urethral strictures examined the use of PRP combined with dexamethasone at the time of internal urethrotomy. After two years of follow-up, stricture recurrence was observed in only 9.5% of patients, and complications were minimal and self-limited. The study also noted that, in cases where recurrence occurred, the resulting strictures were shorter and less severe. These findings suggest that the combined use of PRP and corticosteroids may help support urethral healing and prolong patency following endoscopic treatment.[33]

Molecular pathway modulators: nintedanib and verteporfin

At a molecular level, attention has turned to agents capable of modulating intracellular pathways involved in fibrotic signaling. Nintedanib, a multikinase inhibitor that blocks vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) receptor pathways, acts by suppressing the fibroblast activation and angiogenic signaling that drive urethral scar formation.[34] Verteporfin, a YAP/TAZ pathway inhibitor currently approved for photodynamic therapy in macular degeneration, has shown antifibrotic activity across several preclinical models. Beyond its established effects in Peyronie's

disease tissue, recent studies have explored Verteporfin within urinary-tract and urethral reconstruction contexts.[35,36] In a rabbit urethral reconstruction model, Verteporfin incorporated into a bioactive hydrogel scaffold reduced fibrotic thickening and enhanced epithelial regeneration, supporting its potential to mitigate urethral scarring. Similarly, inhibition of YAP/TAZ signaling with Verteporfin has attenuated fibrosis in renal injury models, further underscoring the pathway's central role in tissue remodeling. While these data highlight the therapeutic promise of YAP/TAZ modulation, dedicated human studies for urethral stricture disease remain lacking, and further translational research is warranted to determine its safety, dosing, and clinical efficacy.[37,38]

Overall, biologic and molecular adjuncts signal a transition toward mechanism-based, regenerative strategies that complement conventional endoscopic management. While early findings are encouraging, rigorous translational and clinical validation is required before these therapies can be adopted into standard practice.

Endoscopic Chemo-Mechanical Therapy

Optilume™ drug-coated balloon (DCB)

Concept and pharmacologic basis

Given the modest success rates and inconsistent outcomes associated with intralesional and instillation-based adjuncts during DVIU, an alternative strategy was developed to improve the durability of endoscopic treatment. The Optilume™ drug-coated balloon (DCB) was designed to enhance clinical outcomes and potentially serve as a minimally invasive alternative to urethroplasty for selected patients. The device combines mechanical dilation of the stricture with localized delivery of paclitaxel, an antiproliferative and antimitotic agent, via its inflatable balloon surface.[39]

Paclitaxel exerts its antifibrotic effect primarily through inhibition of transforming growth factor-beta (TGF-β) signaling during wound healing, thereby limiting fibroblast proliferation and collagen deposition.[40] The drug's pharmacologic properties, including lipophilicity and a prolonged local half-life of approximately three to seven days, enable sustained activity at the dilated stricture site. During balloon inflation, circumferential micro-fissures in the fibrotic tissue facilitate drug penetration into the urethral wall, maintaining therapeutic concentrations throughout the early remodeling phase.[40]

Clinical outcomes and safety profile

Across multiple prospective and retrospective studies, the Optilume™ has demonstrated meaningful and durable improvements in both subjective and objective measures of urethral function. The cumulative findings from the ROBUST trials, along with real-world clinical evaluations and health-economic analyses, support the DCB as a promising alternative to conventional endoscopic treatment, offering sustained efficacy and a favorable safety profile.

In the ROBUST I single-cohort study, 53 men with recurrent, short (<2 cm) bulbar strictures experienced a marked and durable symptom reduction, with mean International Prostate Symptom Score (IPSS) improving from 25.2 to 7.2 at five years.[41] The magnitude of benefit correlated with balloon caliber, as 30 Fr devices achieved superior outcomes compared with 24 Fr.[41] Similarly, the ROBUST II trial reported a reduction in mean IPSS from 18.4 to 6.0 at one year, a 67% improvement among patients with strictures under 3 cm.[42] Objective metrics mirrored these trends: in the ROBUST III randomized trial, Q_{max} improved from 7.6 mL/s at baseline to 12.6 mL/s at two years ($p = 0.003$), while ROBUST I documented a sustained increase from 5.0 mL/s to 19.9 mL/s over five years. Anatomical success, defined as the ability to traverse the treated segment with a 16 Fr cystoscope or 14 Fr catheter, was achieved in 73% of participants at six months in ROBUST II.[41,42]

Long-term data remain limited but encouraging. In the five-year extension of ROBUST I, 29 patients were evaluable; 58% maintained functional success (>50% IPSS improvement), 71% required no re-intervention, and significant gains in Q_{max} (15 mL/s) and reductions in post-void residual volume (82 mL; $p < 0.01$) persisted throughout follow-up.[41] In ROBUST III, the re-intervention-free rate reached 77.8% at two years versus 23.6% in the control arm at one year ($p < 0.001$), underscoring superior procedural durability relative to standard DVIU.[43]

Safety outcomes have been uniformly favorable. Adverse events were typically mild and transient, most commonly hematuria (14%), dysuria (6–9%), and urinary tract infection (6%), and resolved spontaneously without sequelae.[42] No reports of urethral perforation or long-term morbidity were documented across the ROBUST studies. Economic modeling conducted within the UK NHS further supported the DCB's cost-effectiveness, attributing value to its minimal complication profile and reduced need for repeat procedures.[13]

Sexual function data, derived primarily from the ROBUST program, revealed no detrimental effects. International Index of Erectile Function (IIEF) scores

improved modestly at one year, with no change in orgasmic function or new-onset ejaculatory or erectile dysfunction.[41] Semen parameters, including sperm concentration and total sperm count, remained stable. Although paclitaxel has been detected in semen for up to six months post-procedure, with peak levels at one month, protected intercourse is advised during this interval.[41] Notably, a separate cohort of patients treated for radiation-induced posterior stenosis showed no cases of *de novo* urinary incontinence at three-month follow-up.[44]

Collectively, these results suggest that paclitaxel-coated balloon dilation offers a safe, durable, and effective endoscopic option for recurrent urethral stricture disease, combining symptomatic relief with sustained functional outcomes and minimal morbidity. Table 1 provides a comprehensive summary of the aforementioned therapeutic developments and emerging treatment modalities.

Transmeatal Urethral Surgery (TraMUS)

Transmeatal urethral reconstruction has gained attention as a minimally invasive alternative for managing distal and fossa navicularis strictures.[45] This approach avoids external incisions and allows the entire repair to be completed through the meatus, focusing on dissection and graft placement internally. Early clinical experiences have shown that this technique can achieve excellent urinary flow improvement and high patient satisfaction, even among individuals with challenging conditions such as lichen sclerosis, hypospadias, or a history of prior urethral surgery.[46] In one representative cohort, postoperative flow rates improved from approximately 4 mL/s to nearly 20 mL/s, with no recurrence, wound complications, or sexual dysfunction observed during follow-up.[45] Larger multi-institutional analyses have demonstrated success rates approaching 95% at more than a year after surgery, further supporting the reproducibility of this approach. Functional results have also been favorable, with resolution of urinary spraying in many cases and minimal reports of *de novo* symptoms.[47]

Subsequent refinements have incorporated combined dorsal and ventral graft placement, which preserves urethral patency while maintaining a low risk of complications. Reported success rates typically exceed 90% over 18 to 24 months of follow-up.[48,49] These procedures can be completed efficiently without specialized instruments or external incisions, and postoperative catheterization is usually limited to one week. Advantages include reduced morbidity, faster recovery, and simplified suture handling through the transmeatal route.[50] The ability to perform the repair under direct vision without opening the urethra externally also helps preserve vascular supply and minimize tissue trauma, factors believed to contribute to the favorable outcomes and high satisfaction rates associated with this technique.[51]

The continued evolution of transurethral and transmeatal techniques is expected to focus on improving visualization, graft delivery, and precision suturing. The development of dedicated endoscopic instruments and suturing devices has the potential to extend these techniques to more proximal strictures and further reduce operative complexity.[51,52] Parallel research efforts are exploring the biological and mechanical characteristics of urethral fibrosis to optimize graft integration and reduce recurrence.

Tissue Engineering and Regenerative Strategies

Tissue engineering and regenerative medicine offer a promising approach to address the limitations of conventional reconstruction for urethral stricture disease.[53] While substitution urethroplasty using autologous grafts such as buccal mucosa remains the standard of care, its use is limited by donor-site morbidity, restricted graft availability, and variable outcomes in long or recurrent strictures.[54] Regenerative techniques seek to restore urethral integrity by using biomaterial scaffolds, ranging from decellularized extracellular matrices to synthetic or hybrid polymers, seeded with autologous cells such as urothelial, oral epithelial, or smooth-muscle cells. These constructs aim to recreate the layered architecture of native urethral tissue and promote functional regeneration rather than fibrosis.[54,55]

Scaffold-based and cell-seeded constructs

Advances in scaffold fabrication, including electrospinning and three-dimensional (3D) bioprinting, have enabled the creation of constructs with controllable porosity, elasticity, and biological signaling properties. Preclinical data indicate that cell-seeded scaffolds enhance epithelialization, vascularization, and smooth-muscle organization compared with acellular matrices, leading to improved tissue remodeling and patency.[55,56] Smooth muscle cell–based constructs, in particular, show earlier recovery of contractile function, while acellular matrices remain attractive for their

TABLE 1. **Adjunctive endoscopic therapies in urethral stricture disease**

Adjunct Type	Mechanism of Action	Reported Outcomes	Notes/Safety	Ref.
Captopril Gel	ACE inhibitor with antifibroblastic properties; inhibits fibroblast proliferation	Phase II trial: significant recurrence reduction vs. placebo ($p < 0.05$)	Single human study; safety and reproducibility remain unconfirmed	[17]
Intraurethral Brachytherapy (Ir-192)	Localized radiation reduces fibroblast activity and scar formation	94% recurrence-free at 20 months (n = 17)	Limited experience; not replicated; long-term safety unclear	[14]
Botulinum Toxin A	Neuromuscular blockade decreases tension-induced fibrosis	2/3 patients maintained patency > 9 months	Limited data; potential experimental adjunct	[19,20]
Corticosteroids (Triamcinolone, Methylprednisolone)	Anti-inflammatory; reduces fibroblast proliferation and collagen deposition	Longer time to recurrence; modest reduction in recurrence rates	Inexpensive, safe, widely used; good short-term results	[21,24]
Mitomycin C	Antifibrotic; inhibits fibroblast proliferation and collagen synthesis	Lowest recurrence among adjuncts; durable patency	Rare severe complications (osteitis pubis, fistula); injection site critical	[21,22]
Hyaluronidase ± HA/CMC	Degrades extracellular matrix and glycosaminoglycans	53–76% success at 12 months; reduced pain and early recurrence	Often combined with MMC or steroids; minimal complications	[26–28]
Paclitaxel (Drug-Coated Balloon)	Antiproliferative; inhibits TGF-β signaling and collagen synthesis	Q_{max} ↑ to 12–19 mL/s; ~70% re-intervention-free at 5 years	Consistently safe; FDA-approved device	[41–43]
PRP/Mesenchymal Stem Cells	Regenerative; enhance angiogenesis and suppress fibrosis	~90% patency at 24 months	Promising biologic adjuncts; ongoing clinical evaluation; Retrospective series (78 pts) combining PRP + dexamethasone showed reduced recurrence and shorter stricture length upon relapse	[30–33]

Abbreviations: ACE, angiotensin-converting enzyme; Ir-192, iridium-192; PRP, platelet-rich plasma; HA/CMC, hyaluronic acid/carboxymethylcellulose; MMC, mitomycin C; TGF-β, transforming growth factor beta; Q_{max}, maximum urinary flow rate; FDA, U.S. Food and Drug Administration; MSC, mesenchymal stem cell; pts = patients.

accessibility and lower immunogenicity, albeit with less consistent long-term integration.[57]

For clarity, cell-based therapies refer to the direct delivery of viable cells (e.g., stem or epithelial cells) to modulate healing, whereas acellular scaffolds rely on host cell infiltration into a preformed matrix. Biofabricated or bioprinted constructs represent a distinct category in which cells and biomaterials are spatially organized during fabrication to recapitulate native tissue architecture.

A systematic evaluation of experimental studies found that cell–scaffold combinations achieved long-term success rates over five times higher than acellular materials, highlighting the benefit of incorporating viable cells into graft design.[58]

Three-dimensional bioprinting and emerging techniques

Three-dimensional bioprinting represents a major step forward in regenerative urethral reconstruction. By printing bioinks, hydrogel-based materials containing living cells and biomolecules layer by layer, this technology can replicate the complex, multilayered anatomy of the urethra.[59] Hydrogels such

as alginate, gelatin, and decellularized extracellular matrix (ECM) derivatives provide a supportive environment for cell viability and differentiation.[57,59] Gelatin methacryloyl (GelMA) is particularly noteworthy for its tunable mechanical strength and ability to promote smooth muscle proliferation. Incorporating ECM components into bioinks enhances biological cues that guide cell organization and tissue maturation.[60]

Figure 2 illustrates the stepwise workflow of tissue-engineered urethral reconstruction, from autologous cell sourcing and bioink or scaffold preparation, through 3D construct fabrication and surgical implantation, to *in vivo* integration and functional tissue regeneration.

Different bioprinting modalities have been adapted for urethral tissue engineering. Inkjet bioprinting deposits droplets of bioink in precise patterns, while extrusion-based printing extrudes continuous filaments to build robust, cell-laden scaffolds.[61,62] Laser-assisted techniques, which use focused light to transfer bioink without physical contact, achieve high precision and preserve delicate cell structures.[61] Imaging-guided customization using MRI or CT data enables the creation of patient-specific grafts, improving anatomical fit and integration.[59,62]

Preclinical studies using 3D-bioprinted urethral grafts have shown encouraging results, including good vascularization, epithelial continuity, and luminal patency.[63] A number of animal models have demonstrated that bioprinted constructs can approach the mechanical strength and biological behavior of native urethral tissue. Despite encouraging experimental results, clinical translation has not yet led to clinically meaningful progress. Early trials have shown variable outcomes ranging from satisfactory tissue integration to graft contraction and recurrent stricture, underscoring the need for continued refinement of materials, printing techniques, and cell sourcing.[64] Long-term mechanical resilience and functional performance under physiological conditions also require further validation.

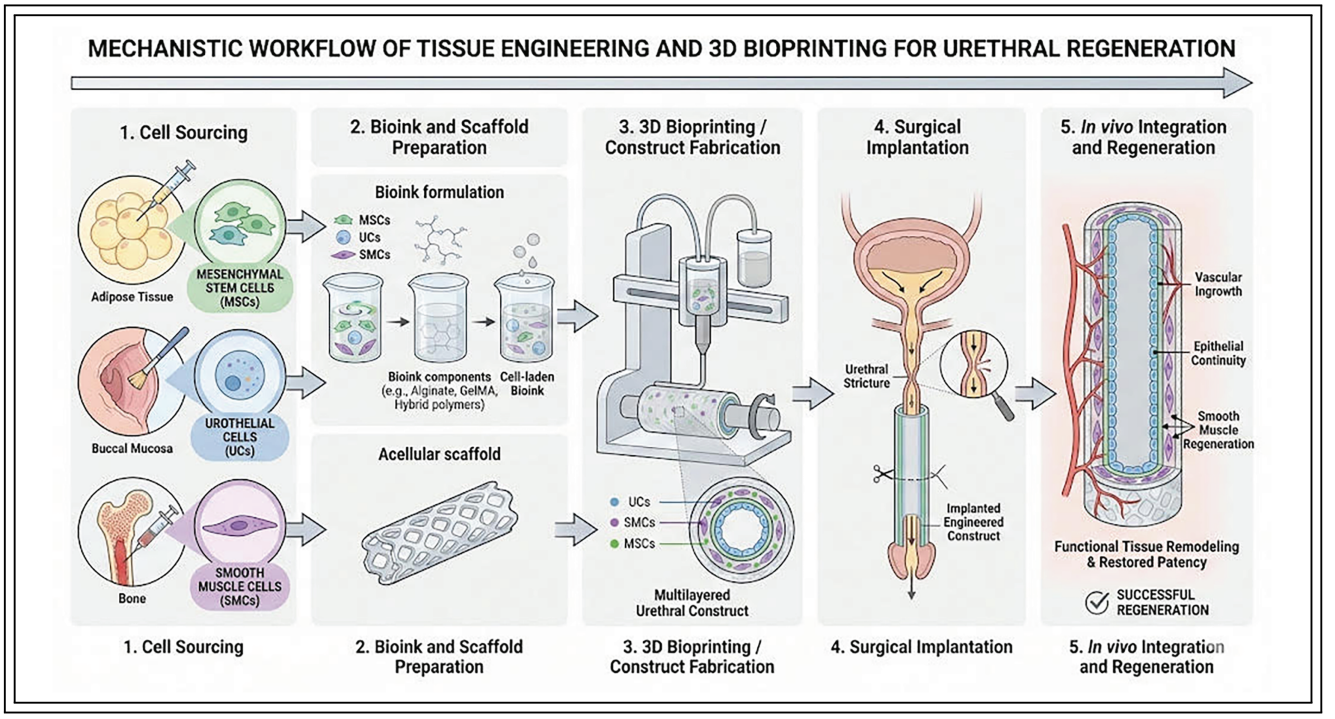

FIGURE 2. Mechanistic overview of tissue engineering and three-dimensional bioprinting strategies for urethral regeneration. Regenerative reconstruction begins with autologous cell sourcing (e.g., mesenchymal stem cells, urothelial cells, or smooth muscle cells), followed by incorporation into bioinks or seeding onto acellular scaffolds. Using three-dimensional bioprinting or advanced scaffold fabrication techniques, multilayered constructs are assembled to replicate native urethral architecture and surgically implanted at the stricture site. Subsequent host-driven vascularization, epithelialization, and smooth muscle regeneration support functional tissue integration and restoration of urethral patency. Note: This image was generated using an AI-based image generation tool (Google Gemini).

TABLE 2. **Ongoing and active clinical trials in urethral stricture disease**

Trial ID	Title	Study Design/Intervention	Outcomes	Status*/Sponsor	Ref.
NCT05463991	Bioengineered Collagen Implant for Urethral Stricture Repair	Interventional, single-arm trial enrolling adult males with anterior urethral strictures; implantation of collagen-based bioengineered scaffold for urethral regeneration	Feasibility, safety, and structure-free rate at 12 months	Recruiting—University of Alberta	[68]
NCT05857371	Recurrent Urethral Stricture Treated by Internal Urethrotomy with PRP Injection	Randomized clinical trial (~60 men); DVIU ± submucosal PRP + dexamethasone injection	Recurrence rate, Q_{max}, and IPSS at 12 and 24 months	Recruiting—Cairo University	[69]
NCT03258658	Autologous Engineered Urethral Constructs for Urethral Stricture	Phase I safety and feasibility study; autologous cell-seeded tissue-engineered grafts for urethral reconstruction	Graft integration, adverse events, and urethral patency	Active, not recruiting—UCSF/Wake Forest Institute for Regenerative Medicine	[70]

Note. *As of November 1st, 2025. Abbreviations: PRP, platelet-rich plasma; DVIU, direct vision internal urethrotomy; Q_{max}, maximum urinary flow rate; IPSS, International Prostate Symptom Score; UCSF, University of California, San Francisco.

Challenges and future directions

Despite technical progress, economic and regulatory factors are also important. Conventional urethroplasty has a median cost of about $7000 and increases substantially in complex cases.[65] Although 3D bioprinting offers the possibility of personalized, donor-free grafts, it remains an expensive and technically demanding process. Broader accessibility will depend on technological maturation, standardization, and economies of scale. Ethical oversight is essential as well, especially in the use of patient-derived or genetically modified cells, requiring clear regulatory pathways for safety and manufacturing quality.[66]

Future work will likely focus on integrating bioactive and antifibrotic components, such as stem cells, growth factors, exosomes, and inhibitors of fibrotic signaling pathways, into bioprinted constructs to further enhance healing and reduce recurrence.[67] Collectively, these advances mark a shift from reconstructive to regenerative urethral surgery, aiming to achieve not just anatomical repair but restoration of normal tissue function.

Table 2 summarizes the currently active clinical trials investigating regenerative and biologic therapies for urethral stricture disease. These studies highlight the translational progression from laboratory-based tissue engineering toward clinical application.

Conclusions

The management of urethral stricture disease has progressed from mechanical and pharmacologic interventions toward mechanism-based, regenerative therapies that aim to restore normal tissue structure and function. Drug-coated balloons represent the most mature example of this shift, combining mechanical dilation with targeted molecular modulation, while tissue-engineered and bioprinted grafts offer the potential for truly biological reconstruction. Looking forward, the integration of regenerative strategies into urethral reconstruction is likely to occur in a stepwise fashion. Chemo-mechanical technologies and pharmacologic adjuncts are positioned for near-term refinement and broader adoption, while biologic therapies may serve as intermediate adjuncts in carefully selected cases. Fully bioengineered or bioprinted urethral constructs remain a long-term objective. Together, these developments

reflect a gradual shift from purely reconstructive surgery toward biologically restorative intervention. Future research should focus on rigorous long-term evaluation, optimization of biomaterials and cellular interfaces, and the integration of these emerging modalities into standardized clinical pathways.

Several limitations of the current evidence base warrant acknowledgment. Many historical adjunctive therapies are supported by small, single-center studies with limited follow-up and a lack of external validation. Even for newer technologies, including biologic and regenerative approaches, available data are frequently derived from nonrandomized studies with heterogeneous outcome measures and relatively short follow-up durations. Definitions of treatment success vary widely across studies, ranging from symptomatic improvement to anatomic patency or need for reintervention, complicating direct comparison between modalities. These limitations underscore the need for standardized outcome reporting, longer-term follow-up, and well-designed randomized trials to define the true clinical value of emerging therapies.

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Authorship Contributions

Nicola Fazaa contributed to the conception of the review, performed the primary literature search, drafted the initial manuscript, and integrated all revisions. Kamil Malshy provided senior supervision, conceptual guidance, critical revision of all scientific content, and oversight of the final manuscript. Ariel Zisman contributed to study conception, provided expert reconstructive input, critically reviewed the manuscript, and supervised the scientific accuracy of the final version. Shadie Badaan and Kirolos Meilika provided clinical expertise, assisted in the interpretation of evidence, and contributed to critical revisions for important intellectual content. Ameer Nsair, Yuval Shafran, Etan Eigner, and Melissa Atallah assisted with literature review, manuscript drafting, and editing across multiple sections of the article. All authors meet ICMJE authorship criteria. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

Not applicable.

Ethics Approval

Not applicable. No patients consent was needed for this study.

Conflict of Interest

The authors declare no conflicts of interest. All coauthors have seen and agree with the contents of the manuscript and there is no financial interest in reporting. We certify that the submission is original work and is not under review at any other publication.

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