Review Article

Update on managing anterior urethral strictures

Constantin Fuehner, Roland Dahlem, Margit Fisch, Malte W. Vetterlein*

Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

*E-mail: m.vetterlein@uke.de

ABSTRACT

A number of techniques have been described for managing anterior urethral strictures in men. In this review, we aimed to summarize contemporary considerations regarding the holistic management of such strictures. The efficacy of reported outcomes is compared to provide evidence-based treatment recommendations. For anterior urethral strictures, durable long-term success rates of >90% may be achieved if the procedure is performed in capable hands at a high-volume referral center, even in recurrent strictures after previous open reconstruction. A one-stage urethroplasty is preferable to avoid a protracted treatment course with multiple interventions after dilation and direct vision internal urethrotomy. Staged urethroplasties are useful in complex anterior strictures providing durable success rates. In addition, perineal urethrostomy represents a valid last resort option with sufficient objective and subjective results. A follow-up evaluation should incorporate objective assessments such as radiographic and functional diagnostics as well as subjective, validated, and disease-specific patient-reported outcome measurement tools to allow for a better comparability and to improve individual risk prediction.

INTRODUCTION

Male urethral stricture is one of the oldest known urological conditions. Urethral reconstruction is continuously challenging, given that treatment decisions may be modified at the last minute, when the patient is already under anesthesia and the stricture reveals a different aspect compared to what was anticipated based on preoperative diagnostics. Thus, a reconstructive urological surgeon requires a broad armamentarium of surgical techniques in order to provide durable treatment outcomes. In urethral reconstruction, it is useful to stratify the urethra according to its main two anatomical segments, given that stricture etiology, treatment options, and outcomes differ significantly between the posterior and anterior urethra. Whereas posterior urethral strictures involving the prostatic and membranous urethra are mostly associated with previous prostate cancer treatments or pelvic trauma, anterior strictures involving the bulbar and penile urethra are commonly congenital or idiopathic, iatrogenic, and inflammatory (i.e., lichen sclerosus associated). Recent research initiatives and surgical advances have enhanced the therapeutical spectrum of anterior urethral strictures and help us to improve our knowledge regarding the natural history and optimal treatment sequencing.

Against this backdrop, the aim of this review is to provide a contemporary summary of considerations regarding the holistic management of anterior urethral strictures, which incorporates the epidemiology and etiology, diagnostics, and several endoscopic and open surgical treatment strategies. Furthermore, we will discuss the value of predicting disease recurrence and underline the current controversies regarding an integral definition of treatment success.

EPIDEMIOLOGY AND ETIOLOGY

There is no universally accepted consensus on epidemiology and anatomic nomenclature of urethral stenoses, strictures, and injuries. In a collaborative effort of the Société

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Internationale d'Urologie (SIU) and the International Consultation on Urological Diseases (ICUD), Latini *et al*. evaluated and reviewed the literature from 1980 to 2010 and suggested the utilization of a standardized nomenclature of the urethra and specifically in the context of reconstructive urethral surgery.[1] According to this consultation paper, the term "anterior urethra" contains the meatus, the fossa navicularis, and both penile and bulbar urethrae. The latter is surrounded by the bulbospongiosus muscle of the corpus spongiosum and is covered by the bulbocavernosus muscle.

To opt for an appropriate type of stricture repair, it is important to understand the cause and etiology of the stricture. There are several known etiologies of anterior urethral stricture disease, which may be categorized into (1) iatrogenic (e.g., history of urethral catheterization or history of hypospadias repair), (2) traumatic (3) inflammatory (e.g., lichen sclerosus associated), (4) postinfectious, and (5) congenital or idiopathic. Of note, the diagnosis of a congenital or idiopathic stricture should only be made in the absence of any other factor, which might have prompted stricture development.[1] Trauma such as pelvic fracture still remains the most common etiology of urethral injury in developing countries but mostly results in posterior urethral injuries. Lazzeri *et al*. evaluated the stricture etiology in 2302 patients treated at a European high-volume center from 1978 to 2014. They found idiopathic strictures to be the most common (38%), followed by traumatic (14%), iatrogenic catheter-related (11%), postinstrumentation strictures (10%), and strictures related to failed hypospadias repairs (17%). Importantly, urethral stricture etiology does affect treatment outcomes significantly,[2] and thus, it is crucial to evaluate the etiology when interviewing a patient before therapy planning. According to the ICUD, there are no direct measures of the true incidence but is estimated at approximately 0.6% of an at-risk male population.[1,2]

DIAGNOSTICS

In patients with anterior urethral strictures, diverse diagnostic modalities are available for preinterventional evaluation. To determine the most adequate procedure type, the length of the stricture, its etiology, and previous interventions and procedures must be considered. The endoscopic finding of a narrow, nonpassable stricture rarely provides sufficient information to guide effective treatment algorithms. Retrograde urethrography (RUG) still remains the gold standard to evaluate anterior urethral strictures and may be combined with a voiding cystourethrography (VCUG) to gain information on the patency of the posterior urethra, which is commonly masked during RUG due to involuntary contraction of the external sphincter. A well-conducted radiographic imaging will identify the location and length of a stricture as well as further associated pathologies with good sensitivity and specificity.[3,4] If a patient had undergone recent urethral manipulation such as catheterization, urethral rest of 4–12 weeks for sufficient tissue recovery after the manipulating event is recommended, as otherwise, the full extent of the stenosis will not be manifested in urethrography and the true extension of the stricture will be underestimated.[5] Rigid or flexible urethrocystoscopy may serve as an adjunct procedure to re-evaluate abnormal findings during urethrography.[6] Noninvasive diagnostic tools such as a standardized symptom assessment (International Prostate Symptom Score questionnaire) or uroflowmetry were found to have additive value to imaging or urethrocystoscopy but should not be used to diagnose or exclude a urethral stricture.[6] In recent years, patient-reported outcome measurement (PROM) tools have gained in importance regarding the subjective evaluation of treatment-related outcomes from a patient's vantage point.[7,8] As of now, only one urethral stricture-specific PROM questionnaire has been developed,[9] expanded, and externally validated.[10] For bulbar and penile urethroplasties, significant improvement in all the included domains was shown in 46 men before and 2 years after surgery.[11] In a recent collaborative effort, an advanced disease-specific PROM tool is currently being validated to create the novel Urethral Stricture Symptoms and Impact Measure 32-item instrument.[12] A remarkable strength of this novel tool will be the incorporation of both physicians' and patients' perception regarding the prioritization of disease- and treatment-related complaints and symptoms.[8,12]

DISEASE MANAGEMENT

Dilation, urethrotomy, and stents

Endoscopic treatment of urethral stricture disease can be easily performed because of its simplistic transurethral approach, minimal resource requirements, low morbidity, and minimal invasiveness compared to open urethral reconstruction. This is mirrored by the findings from several surveys in Europe and the US, revealing that the most common procedures among practicing urologists to treat anterior urethral strictures are dilation (56%–93%) and direct vision internal urethrotomy (DVIU; 66%–97%).[13-16] Furthermore, most urologists (58%–77%) do not perform urethroplasties on a regular basis[13-16] even though it still remains the most definitive treatment of urethral stricture disease. To ensure durable urethral patency, it is crucial that re-epithelialization occurs prior to the development of severe wound contracture.[17] This leads to stricture-free survival rates after endoscopic treatment of roughly 70% for highly selected patients (primary bulbar stricture, <1 cm)[18] versus 90%–95% stricture-free survival after excision and primary anastomosis (EPA).[19,20] Buckley *et al*.[21] recently reviewed the literature on dilation, DVIU, and stenting. The ICUD classified all included articles using the Oxford Centre for Evidence-Based Medicine criteria and drafted treatment recommendations. It is advised to use DVIU or dilation as a first-line therapy for short (i.e., <1–2 cm), isolated bulbar urethral strictures depending on the available infrastructural

resources. A repeat endoscopic treatment may be offered for favorable strictures with recurrence occurring later than 3 months after primary treatment. Further, they opined that repeat (i.e., more than two procedures) DVIUs or dilations should not be recommended, given that recurrence rates significantly increase with each repeat endoscopic procedure.[22-24] Therefore, minimally invasive procedures such as intermittent catheterization and repeat DVIU or dilation may be used as a palliative maneuver only in patients with no further available open surgical options.[21] Different modifications such as the addition of lasers, for example, did not lead to improved success rates.

Recently, the use of endoscopic repair with adjunct antifibrotic agents was investigated to improve recurrence-free survival. However, these options are still in an experimental status and require continued research and longer follow-up data.[25] The use of urethral stents such as UroLume™ or Memokath™ is not recommended due to a high complication rate (up to 55%) such as stent obstruction, stent migration, or recurrent strictures as well as the need for explantation and subsequent complex and challenging urethral reconstruction.[26-29]

Substitution urethroplasty

A number of different grafts have been used in reconstructive urethral surgery including the penile skin, scrotal skin, extragenital skin, oral mucosa, bladder mucosa, and colonic mucosa.[30,31] Oral mucosa contains many of the ideal graft characteristics for urethral reconstruction and therefore may be considered the gold standard for augmentation.[30-32] Oral mucosa is superior over the skin as a substitution material in both penile and bulbar urethral strictures.[33,34] One reason for its durability is that it retains its histopathological characteristics and is not overgrown with urothelium after urethral engraftment and urine exposure.[32] Compared to the bladder, rectum, and skin, it has a thick epithelium to provide durability and is less prone to contracture or sacculation. Furthermore, it has a thin lamina propria making it more receptive to expeditious neovascularization.[35,36] From a technical standpoint, it can be easily harvested with minimal morbidity and thus characterizes a safe procedure with high patient satisfaction.[37]

There are different approaches to the onlay augmentation procedure, which may be performed through a ventral, dorsal, or lateral approach. However, to date, there is no conclusive evidence of the benefits of one over the other available.[31,38] As a technical advancement for predominantly penile stricture with a significant lack of ventral tissue coverage, Asopa *et al*. described a ventral sagittal urethrotomy approach with placement of a dorsal inlay graft.[39] In 2008, Palminteri *et al.* suggested that a ventral onlay might be placed as an adjunct of a dorsal inlay graft.[40] These new techniques significantly expand the reconstructive surgeon's choices, and durable success rates of up to 90% may be reached.[40,41] Mangera *et al*. performed a systematic review of over 2000 urethroplasties between 1985 and 2011. When considering the bulbar urethra, there was no significant difference in treatment success between the dorsal (88%) and the ventral onlay procedures (89%), respectively. Taken together, whether a graft is placed dorsally, ventrally, or laterally does not change the surgical outcome significantly if it is performed in capable hands. To date, there are no randomized controlled trials (RCTs) to investigate the superiority of one graft technique over the other. In a prospective case–control study from 2014, the authors found no difference between dorsal inlay and dorsal onlay grafts in patients treated for long anterior strictures.[42] An RCT is currently recruiting and aims to compare the dorsal versus the ventral onlay approach in patients with bulbar urethral strictures >1 cm (NCT02634619), and the results are awaited for 2020. Up until then, surgical grafting techniques should rely on the surgeon's expertise and preference as reported outcomes with different procedures are comparable.[30,38]

When dealing with different stricture etiologies, for example, those following radiation therapy or particularly high-risk patients with long strictures, a ventral approach may be the best choice, because it can be supported by a gracilis muscle flap, supporting the mucosa with a healthy graft bed.[43] Similarly, in patients with lichen sclerosus-associated strictures, oral mucosa is currently considered the substitution material of choice, given that inflammatory strictures tend to be longer and recur more frequently because of exacerbation of the underlying disease process. Since oral mucosa has a privileged immunology, skin tissue has a higher rate of lichen sclerosus recurrence. One-stage oral graft urethroplasty showed great success in patients with lichen sclerosus in penile (100%) and bulbar reconstructions (91%).[44] In summary, oral mucosa is a versatile augmentation material, and in experienced hands, the success of oral mucosal graft for urethroplasty is similar regardless of the technical approach. Although there are subtle theoretical benefits for each surgical technique over the other, data have not supported a significant long-term difference in treatment success. Overall, surgeons should choose a technique with which they feel comfortable and experienced.[30]

Several studies on bioengineered oral mucosa and other grafts have been performed but still must overcome existing obstacles. In the future, tissue engineering might be of use, particularly for complex strictures, where long segments of oral mucosa would be required or when the use of oral mucosa is not indicated, but to date, experimental techniques should not be used outside an ethics committee-approved clinical trial.[31,45]

Excision and primary anastomosis

EPA characterizes a reconstructive surgical technique in which a narrowed urethral segment and the corresponding

spongiofibrosis are excised and the two healthy urethral ends are re-approximated.[46] Success rates after EPA are excellent, but the indication of EPA ought to be made wisely. Different anatomic features have to be considered when choosing the most adequate surgical approach.[47] EPA is rarely an option in the penile urethra because of consecutive penile shortening, which might eventually imply postoperative penile curvature. In bulbar strictures, the treatment decision mainly depends on the length of the stricture, given that tension on the re-anastomosed urethra after EPA may also prompt penile curvature after excessive urethral excision.[48] The appropriate maximal stricture length, which might be approached by EPA, ranges from 1 to 4.5 cm.[19,49-51] The impact of EPA on postoperative erectile dysfunction after anterior urethroplasty is controversial. While the SIU/ICUD consultation on urethral strictures and other authors do not attach too much importance to the association of EPA and postoperative erectile dysfunction,[46,52,53] there are some studies showing a significant impairment. Barbagli *et al*., for example, reported non-negligible postoperative occurrence of patient-reported sexual dysfunction in terms of ejaculatory disorders, cold or soft glans syndrome, and decreased glans sensitivity.[20] Another study reported on the occurrence of chordee (44%) and decreased penile length (22%) in men with strictures >2.5 cm.[54]

In order to avoid the full-thickness transection of the corpus spongiosum and restrict the trauma during EPA, Jordan *et al*. introduced the vessel-sparing or nontransecting EPA,[55] which was modified by Andrich and Mundy[56,57] and has been incorporated into clinical practice.[58-61] To date, however, there is no clear evidence of a superiority of the nontransecting approach over conservative transecting EPA regarding postoperative sexual and erectile functions,[61] but both approaches appear to be equally effective regarding stricture recurrence-free survival and perioperative safety.[59-61]

In summary, EPA may be safely performed in men with short and isolated bulbar stricture with sufficient success rate of >90% and insignificant morbidity.[46] To date, the impact of EPA on postoperative sexual function remains unclear.

Staged urethroplasty

Stricture treatment by staged reconstruction has been mostly replaced by one-stage approaches such as EPA or graft augmentation. The conventional two-stage procedures were developed in the 1950s and based on marsupialization of the stricture followed by a second procedure after wound reconvalescence. In earlier days, penile shaft skin or scrotal skin was used, but outcomes were poor, and the presence of hair follicles in the neourethra triggered complications. Contemporary staged urethral reconstruction incorporates hairless grafts such as oral mucosa or split-thickness skin grafts. Staged procedures can play a vital role in urethral reconstruction as one-stage urethroplasties are prone to relatively high complication rates after failed hypospadias repairs,[62] and oral mucosa may only be used if viable urethral tissue is present and if strictures do not exceed 10 cm in length due to marked oral morbidity. Other factors, which may be indications for staged procedures, are inflammatory etiology with presence of lichen sclerosus or a patient with multiple previous open surgeries. Similarly, staged procedures may be preferred if there is a lack of sufficient tissue to cover the graft in multiple layers to prevent fistula formation. While there is no clear evidence of a superiority of staged approaches in bulbar strictures, they may be more useful for treatment of complex penile strictures, specifically in hypospadias- or lichen sclerosus-associated strictures. Hence, the SIU/ICUD suggests staged urethral reconstruction with oral mucosa after a complete excision of scar tissue to provide the best results in patients with penile stricture in such cases.[38,45] Similar to one-stage procedures, there are several options of grafts for use in staged urethroplasty. Pfalzgraf *et al*. compared the outcomes of patients after staged urethroplasty with oral mucosa and split-thickness skin grafts (mesh graft urethroplasty).[63] Overall success was 84% at a follow-up of roughly 1 year with no difference between graft types. Patients also reported adequate postoperative ejaculatory function (68%) and treatment satisfaction (79%), and no severe complications were noted.[63] Other studies with higher number of participants also showed excellent success rates and low short- and long-term morbidity.[64] In a recent multi-institutional study from the Trauma and Urologic Reconstruction Network of Surgeons, patients undergoing staged penile urethroplasty with oral mucosal graft for complex penile strictures showed similar results with minimal changes in erectile and ejaculatory postoperative functions.[65]

STRICTURE RECURRENCE

Predicting and defining stricture recurrence

The ability to compare outcomes between different techniques has been hampered by the lack of standardized definitions of success and follow-up. The basic goal of a surgeon in urethral reconstruction is to provide a patent urethral lumen allow for sufficient urine flow. On the other hand, recent studies have shown that postoperative patient satisfaction does require not only a decrease of urinary complaints but also an absence of pain and sexual side effects.[66] Erickson and Ghareeb proposed a definition of success and a follow-up strategy after reviewing literature on earlier definitions of surgical success.[67] They advised to evaluate treatment outcomes at 3 weeks after surgery with a combined RUG and VCUG. Apart from radiographic outcomes, functional diagnostics such as standardized, validated questionnaires and an anatomical assessment by uroflowmetry or urethrography at regular intervals are recommended. However, whether a regular endoscopic calibration (flexible cystoscopy) is a useful tool to improve

health-related quality of life by detecting an anatomical recurrence at an earlier time point remains a matter of debate. Recently, we evaluated the impact of an early postoperative standardized radiographic and functional voiding trial after one-stage oral mucosal graft urethroplasty on stricture recurrence in 513 patients.[68] The main finding of this study was the significant predictive value of such early postoperative voiding trial results regarding long-term outcomes. Patients who failed radiographically (residual narrowness) or functionally (postoperative Qmax <preoperative Qmax or postvoid residual volume >100 ml) fared significantly worse in terms of stricture recurrence. Interestingly, there is no consensus to date whether extravasation at an early urethrography impacts long-term outcomes and this seems to be dependent on the surgical technique used in the first place.[68,69]

To date, several risk factors of stricture recurrence have been identified and are mostly derived from multivariable analyses. For example, stricture length, patient comorbidity, obesity, and infectious etiology were associated with stricture recurrence in a single-center study.[70] Medical conditions such as diabetes and tobacco use are known to cause microvascular damage, which could impede healing after urethroplasty and promote stricture reformation. The same is true for lichen sclerosus, a history of pelvic radiotherapy, and hypospadias.[71,72] Taking the same line, several studies have shown the importance of the surgical sequence (i.e., a history of previous endoscopic or open reconstruction) as a risk factor of recurrence in various populations.[72,73] On a histopathological level, sclerosis was found to be a significant predictor of stricture recurrence in a recent study evaluating resected urethral stricture specimen.[74] Thus, it seems important to excise the fibrotic tissue completely during primary surgery in order to diminish the risk of recurrence. Identifying individuals at highest risk of early recurrence may guide follow-up protocols in selected subsets of patients. In conclusion, the factors that lead to urethroplasty failure are still not fully understood and further research is needed.

Recurrence management

In patients with urethral strictures that recur within 6 months or are refractory to a second DVIU or dilation, open urethral reconstruction should be generally offered as a definitive treatment strategy.[21] Treatment failure following the previous urethroplasty is somewhat more intricate. Recurrent strictures after previous open reconstruction are longer and require more complex interventions, and repeat or secondary urethroplasty has enhanced the surgical armamentarium in recurrent strictures following the previous urethroplasty.[75] The favored surgical approach in recurrent strictures is subject to geographic differences: whereas EPA is favored as a relapse procedure in the Anglo-American area, repeat oral mucosal graft urethroplasty is most favored in Europe. Nonetheless, in both EPA[75,76] and oral mucosal graft urethroplasty,[73] treatment outcomes were comparable in the repeat compared to the primary setting. Thus, there is no standardized recommendation regarding repeat urethroplasty techniques, and treatment decisions should be made on an individual basis.[75] However, it has been clearly shown that the success rates after repeat urethroplasty are significantly higher compared to DVIU following urethroplasty, which do not exceed 40%–60%.[77-79] DVIU may be an adequate treatment option in cases of a short and focal stricture recurrence at the proximal or distal end of the former graft or EPA after open reconstruction.[80] Subtle differences could be shown in favor of DVIU after graft substitution compared to DVIU after EPA.[79] However, the risk of recurrence in this setting is relatively high at up to 50% even after a short follow-up period.[78] Therefore, DVIU may only be offered to unfit patients or those not willing to undergo immediate open surgical revision. In patients with a history of multiple and failed therapies and for older and comorbid patients who are reluctant to undergo a protracted treatment course, perineal urethrostomy is a viable last resort option with PROM outcomes comparable to those of long stricture anterior urethroplasty.[81]

CONCLUSIONS AND FUTURE PROSPECTS

Increasing research initiatives and studies of improved quality including larger sample sizes have improved our knowledge on etiology, diagnostics, and treatment algorithms for anterior urethral stricture disease. Depending on the etiological background and the treatment choice, durable long-term success rates of >90% may be achieved if the urethral reconstruction is performed at a high-volume referral center with the full reconstructive armamentarium available. However, there is a worrisome lack of Level I evidence regarding the superiority of one surgical technique over the other, refinement of treatment algorithms, or the impact of different treatment approaches on both objective and patient-reported outcomes. Future research will have to set the focus on the planning and realization of multi-institutional, well-designed RCTs and prospective longitudinal assessment of refined and disease-specific PROM outcomes and how they change over the time of the treatment course.

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