



Urethral Pain Syndrome: A Systematic Review

Mashrin Lira Chowdhury¹ · Naila Javaid¹ · Gamal M. Ghoniem¹

Published online: 16 April 2019

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Purpose of Review Urethral pain syndrome (UPS) is defined as pain localized to the urethra with an unpleasant sensation, dysuria often accompanied by urinary frequency and urgency present greater than 6 months in the absence of an identifiable cause. A paucity of information exists on the subject as it is often combined with conditions such as interstitial cystitis or prostatitis. The aim is to provide and explain different definitions and diagnostic work-up and discuss treatment options for providers.

Recent Findings Few recent studies exist addressing urethral pain syndrome. Most literature is decades old. Thirty-five full-text articles were included in the review. This syndrome occurs most commonly in females of childbearing age. Patients must be evaluated thoroughly with full history and physical. Etiologies proposed include sensory dysfunction, pelvic floor dysfunction, psychogenic factors (depression and anxiety), diet, obstruction, infections, and hypoestrogen status. Treatment strategies include behavioral management of stress management, diet modification, pelvic floor treatments, local estrogen, anesthetic with or without cooling, oral medications for related lower urinary tract symptoms, or anxiolytics/antidepressants. Psychological support is recommended for these patients.

Summary UPS can have multiple etiologies and a multimodal therapy should be applied to these patients. Therapy should be individualized, oftentimes including concurrent therapy for overlapping conditions. Serious pathology should be ruled out and a stepwise approach to treatment should be utilized after setting treatment expectations with the patient.

Keywords Urethral pain · Dysuria · Non-infectious urethritis · Urethral syndrome

Introduction

Urethral pain syndrome (UPS), previously known as “urethral syndrome,” has been described in literature as early as the 1930s. The International Continence Society defines UPS is as pain localized to the urethra, chronic dysuria, an unpleasant feeling in the urethra, often accompanied by urinary frequency and urgency in the absence of an infection or other identifiable cause for a period greater than 6 months [1•, 2]. Pain can have physiologic and psychological impact on all domains of a patient’s life leading to poor sleep, anxiety, depression, and poor performance [1•]. In the current time where chronic pain and pelvic pain syndromes are gaining attention in our practice, UPS may be considered a separate condition from

interstitial cystitis, chronic prostatitis, and pelvic pain syndromes. [2]

Gallagher et al. in 1965 was one of the first that brought to attention the symptom complex and summarized different etiologies of inflammation, paraurethral gland atrophy, obstruction, and even anxiety [3]. Zufall in 1963 concluded that this syndrome is not a true organic disorder in the urethra, but rather a condition that is “mainly psyche in origin... possibly hysteria and anxiety neurosis” [4]. In a recent paper, UPS falls into a Somatic Symptom Disorder category when it persists for at least 6 months [5]. While there is little doubt that a psychological component to the illness exists and many patients suffer in pain for many years, the authors of this paper believe there may be several compounding causes of UPS. Most of the studies on UPS are older and a paucity of contemporary studies exists making the diagnosis and treatment of UPS difficult.

A 1980 study suggested that UPS accounts for 5 million office visits in the USA [6]. Unfortunately, it is difficult to ascertain the true burden of UPS because it is a condition that often gets misdiagnosed. It has been suggested that the true prevalence is underreported due to the similarity of symptoms

This article is part of the Topical Collection on *Inflammatory/Infectious Bladder Disorders*

✉ Gamal M. Ghoniem
gghoniem@uci.edu

¹ University of California, Irvine, Orange, CA, USA

between UPS and other pelvic pain conditions [7]. It may actually occur in up to 20–30% of all adult women, and it is most common in Caucasian females of reproductive age [8]. The diagnosis and treatment in male patients is difficult and may overlap with chronic prostatitis. The authors of this paper will focus on the treatment of females since UPS is more commonly described to be a female syndrome.

Methods

This is a systematic review performed by following PRISMA guidelines searching online electronic databases (PubMed, Cochrane, Medline, Embase) and recent articles published by the MAPP network from January 2013 to September 2018 by two researchers MC and NJ. The search was then expanded through reading current literature and referencing relevant articles from the bibliography (Fig. 1). Key terms

used in the search included “urethral syndrome,” “urethral pain,” “urethral pain syndrome,” “non infectious urethritis,” or “chronic dysuria.” American Urologic Association (AUA) Updates, AUA Guidelines, American Urogynecologic Society (AUGS), International Continence Society (ICS), British Medical Journal (BMJ) Best Practice and European Association of Urology (EAU) were also searched for relevant guidelines. A total of 35 papers were included in the review. Papers relating to male patients, prostatitis, bladder pain syndrome, and interstitial cystitis without discussion of urethral pain were excluded. Analysis, interpretation, and construction of the review was conducted by all three authors of the paper.

Presentation

The typical patient who presents for evaluation of UPS is a Caucasian female of reproductive who presents with urethral pain and in many instances has been seen by multiple

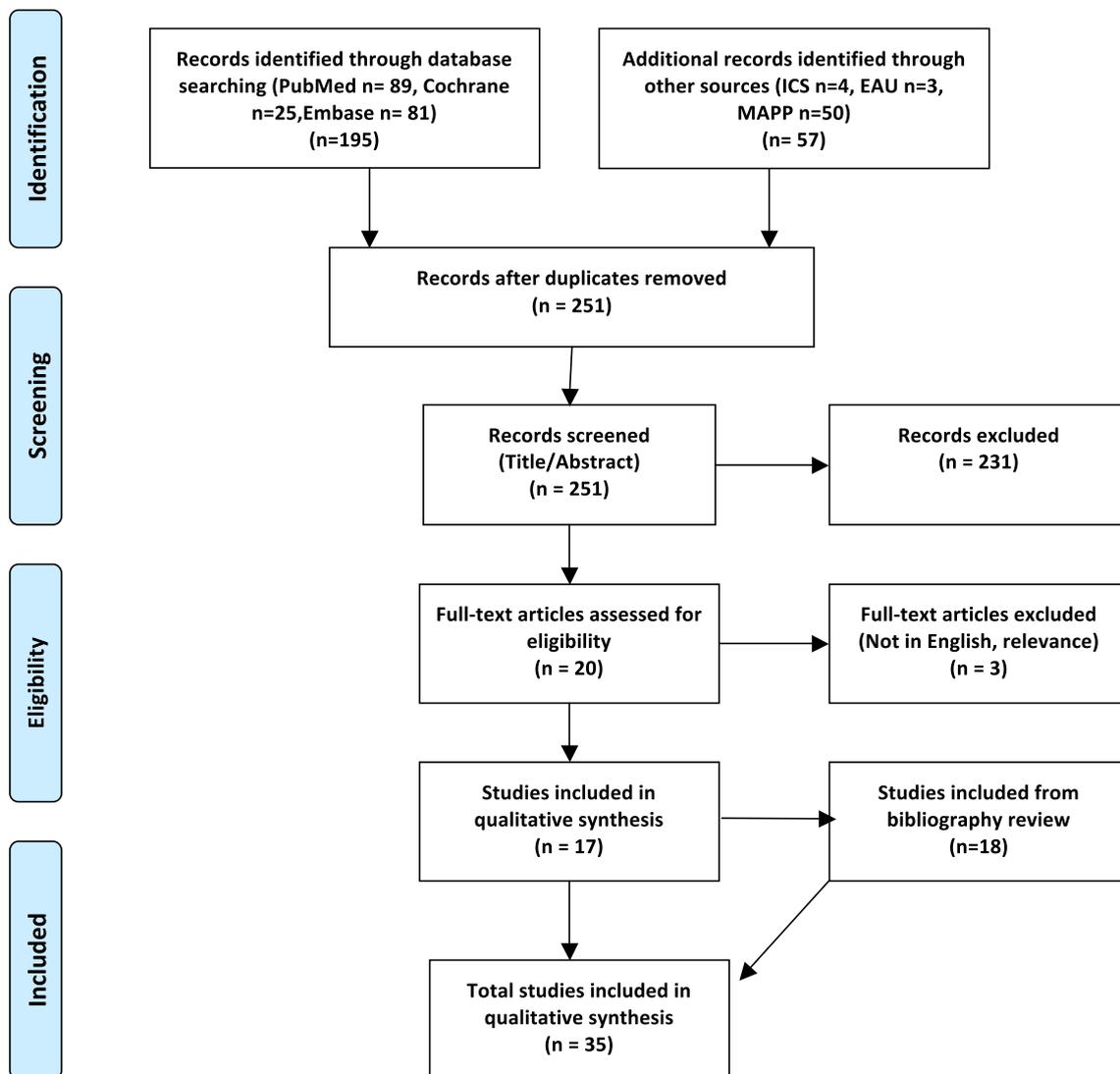


Fig. 1 PRISMA flow diagram

providers. Pain episodes may occur intermittently, and some patients may identify triggers for these episodes. Many also suffer from other pain or allergy disorders including fibromyalgia, vulvodynia, irritable bowel syndrome, chronic fatigue syndrome, or allergies [9]. They may have been diagnosed with urethritis and treated with multiple courses of antibiotics. They may have undergone extensive gynecological workups. Many have undergone multiple urethral dilations, which are usually ineffective. Clemens et al. from the MAPP Network found that in a cohort of patients with urological chronic pelvic pain syndromes, women were more likely to contact providers, have more office visits, and more often undergo procedures and medication changes. Patients who reported more pain and higher depression scores also exhibited more of these “healthcare-seeking behaviors.” This surely fits our demographic of the UPS patient [10].

Diagnosis

Diagnosis can be difficult as the etiology is multifactorial and requires a multifaceted approach. A thorough history should be obtained including past medical, surgical, family, and social histories including a gynecologic and sexual history. Recent changes in the patient’s physical health, medications, medical diagnoses, major life events, or life stressors should be noted. The patient’s sexual function should be assessed as UPS and sexual dysfunction can go hand in hand. It is imperative to know if the patient has been treated for recurrent UTIs, stone disease, chronic constipation or diarrhea, or if they have a history of pelvic surgeries or injuries. A Visual Analogue Scale (VAS) or Likert Scale can be utilized for objective assessment. An internal and external physical exam should be performed in all patients. In addition to the genitourinary and gastrointestinal exams, a neurologic and musculoskeletal exam should be included [11].

A systematic approach to the exam should be undertaken starting with the general appearance of the patient. Does he/she look anxious or disheveled that could indicate an underlying psychological issue? Check the abdomen for scars of previous surgeries. Palpate for tenderness or masses. Inspect the patient’s posture and gait for presence of back pain. An external genital exam includes commenting on the general appearance of the vagina in females, presence of atrophy, obvious pelvic organ prolapse, or masses. Palpate the labia and introitus for vulvodynia, exaggerated tenderness to palpation or hyperesthesia. A pelvic exam will allow for evaluation of the different components of the vagina including apical, anterior, and posterior [9]. Palpate the urethra specifically in the midline and note the presence of discharge, masses, or tenderness. A bimanual exam will tell you if there is pelvic floor spasms or presence of trigger points elicited by pain.

Since UPS is often a diagnosis of exclusion, obvious causes of lower urinary tract pathology must be ruled out. This

includes ruling out urinary tract, vaginal and sexually transmitted infections (STIs), local causes such as atrophic vaginitis or Bartholin’s gland cysts or infections. Other things like bladder outlet obstruction, stone disease, tumors, endometriosis, and constipation should be ruled out. A urinalysis and culture as appropriate with a post void residual will rule out infections and urinary retention. STI, vaginal, ureaplasma, and mycoplasma cultures should be sent if appropriate. Other useful tools to narrow down the diagnosis include a bladder diary, renal/bladder ultrasound to look for stone disease, MRI pelvis to look for urethral diverticulum, urodynamics testing to assess bladder capacity and function, and cystourethroscopy with or without bladder biopsy can be utilized as appropriate [12].

Etiology

There have been many proposed etiologies for urethral pain syndrome and we will review each one carefully.

Sensory Dysfunction

UPS may result from neuropathic hypersensitivity after an episode of UTI. A small group of patients with grand multiparity were associated with UPS. It is not known if the pain felt by patients with UPS is “an abnormal perception of a normal stimulus or a normal perception of an abnormal physiologic sensory stimulus” [1•, 13•]. A study on cats with IC found that the lamina propria of the bladder and urethra undergoes remodeling due to chronic inflammation. This in turn alters the communication of sensory information of the bladder and urethra through the epithelium, nerves, and muscles [14]. In UPS, it seems that there is a neurologic dysfunction in which abnormal processing of sensory information causes pain in the urinary tract. Thus, patients experience pain that is “out of proportion to a demonstrable pathology” [15]. Vulvodynia and paraurethral gland inflammation has also been suggested to refer pain to the urethra [1•].

Pelvic Floor Dysfunction

Urethral pain episodes may coincide with involuntary spasms and voluntary tightening of pelvic floor muscles [16]. This produces a vicious cycle in which the original cause of the pain produces pelvic floor tension, but once the original cause of the pain is cured, the pelvic floor dysfunction persists which in turn augments the pelvic floor tension. This theory was further supported by a publication in 2016 that found that chronic pelvic pain stimulates tonic contractions of pelvic musculature, which in turn perpetuates the chronic pain. This may be a reason why UPS becomes refractory to treatment. Moreover, because there is “cross-talk between pelvic floor and bladder and bowel neurons in the spinal cord,” the

pelvic floor dysfunction can produce symptoms of voiding dysfunction such as urinary urgency and frequency [15].

Philip et al. reviewed various studies on external urethral spasms and increased urethral closure pressure as seen on urethral pressure profilometry. This was previously treated with dilation, alpha-blockers, or muscle relaxants [8].

Psychogenic Factors

Some studies suggest that UPS may be a physical response to a psychological condition. A study in 2014 found that patients with UPS score significantly higher on the hypochondriasis, hysteria, and schizophrenia scale. Moreover, patients exhibited exaggerated concerns over their body feelings [8]. Patients with urethral pain syndrome often demonstrate high levels of anxiety and depression perhaps suggesting a link [16]. On the other hand, depression and anxiety may be a by-product of the failure to adequately manage this painful condition. This suggests that patients need counseling and/or referral to a specialist.

Diet

Some studies propose that certain foods can behave as triggers for pain episodes [9]. In 1972, Powell et al. found that 900 women exhibited improved symptoms after refraining from citrus fruits, pepper, condiments, nuts, cocoa, and tomatoes [17]. A subsequent study in 2002 on 675 women with UPS found that elimination of hot and spicy food, caffeine, and alcohol from the diet for 12 weeks resulted in at least 80% improvement of all symptoms for 89% of the subjects [18]. Thus, another potential etiology for UPS is dietary impact of irritation to the urinary tract, which in turn exacerbates the inflammation.

Bladder Outlet Obstruction

Bladder outlet obstruction from anatomic or functional reasons can lead to high pressure voiding, turbulent flow, and referred pain. The Lyon's Ring Theory proposes that an "anomalous congenital fibrous band encircling the female urethra just proximal to the external meatus may cause urethral stenosis in girls" [19]. A study in 2017 noted that the most common acquired causes of urethral stricture were previous urethral instrumentation (including traumatic catheterization), followed by traumatic vaginal delivery and idiopathic causes [20]. Infections (Gonorrhea, TB) or radiotherapy can contribute to intraluminal urethral fibrosis [19].

Infectious

Urinary tract infections and sexually transmitted infections are known causes of dysuria. An inflammatory environment

provides a medium for bacteria that are usually commensals to flourish and become pathogenic over time, thus a culprit for UPS.

A positive urine culture, indicating greater than 10^4 organisms, excludes the diagnosis of UPS. However, this does not mean that infection does not play a role in causing UPS. Higher rates of *Ureaplasma urealyticum* and *Chlamydia trachomatis* were found in patients with UPS compared with controls [21]. Moreover, a study in 2014 found that most cases of non-specific urethritis are due to *Mycoplasma genitalium* [22]. These are fastidious bacteria that do not grow readily on media that are routinely used for urine culture [8].

The female paraurethral glands are homologs to the male prostate, which is why UPS can be considered "female prostatitis" similar to NIH Category III chronic prostatitis males [23]. UPS may initially develop from an infection in the paraurethral glands, and when this infection becomes prolonged, chronic inflammation develops and leads to deleterious neurologic changes that produce pain [21]. The theory that infected paraurethral glands leads to UPS dates all the way back to 1931 [19].

Hypoestrogenism

Estrogen receptors are found within the trigone and urethra in females; thus, a relative hypoestrogen state can cause hypersensitivity within the vagina and urethra. Deficiency of estrogen can aggravate symptoms of UPS, and postmenopausal women may benefit from local estrogen therapy [8].

Treatment

Pain can have multifactorial causes, and the approach as we know for other genitourinary (GU) pain disorders should take a multimodal approach including addressing visceral, musculoskeletal, emotional, sexual, and behavioral domains [11]. According to the European Association of Urology (EAU), treatment for urethral pain syndrome must be multidisciplinary and take a "trial-and-error" approach. This condition is notoriously difficult to manage and exhibits a high failure rate, with many treatments becoming refractory over time. Thus, the goal of therapy should be focused on minimizing pain and improving the quality of life. Before executing any treatment plan, expectations should be set with the provider and patient regarding the treatment goals. Identifying which aspects are most important to the patient can help guide the plan and be more successful. It is important to set up the long-term follow-up plans and even include multiple disciplines from the beginning [11]. Moreover, a "one-size-fits-all" approach is not adequate, and management plans must be tailored according to each patient's unique presentation. Finally, the therapeutic guidelines for UPS should mirror the guidelines for IC/BPS as recommended by the AUA:

conservative therapy should be initiated first, gradually followed by more invasive interventions. [24]

Behavioral Management

Stress Reduction First line for chronic pain syndromes includes behavioral strategies to decrease triggers. Anxiety, depression, and sleep habits should be addressed especially if the patient is sleep deprived. Implementation of stress reduction activities such as yoga and meditation should be emphasized [9, 16]. Daily sitz baths with Epsom salt is encouraged as well.

Diet Studies have found that the removal of irritants, from the diet can reduce inflammation in the urinary tract [18]. Thus, it is recommended that patients with UPS eliminate the following from their diet: caffeine, alcohol, hot and spicy foods, and high-acid fruits. Supplementation with sodium or potassium bicarbonate may provide some benefit [16]. In addition, many patients often restrict water intake due to urinary frequency. Patients should be advised to increase water intake because concentrated urine is more acidic and contains a higher concentration of irritants, especially potassium, which can exacerbate dysuria.

Pelvic Floor Treatments

Therapies that alleviate pelvic floor dysfunction include pelvic floor muscle therapy and/or biofeedback [16]. A study in 2017 also found that botulinum toxin injections into the pelvic floor muscles reduce urethral pain and increase urine stream [25]. Patients should be counseled that botulinum toxin injection can lead to urinary and/or flatule incontinence. Treatment of levator ani trigger points with bupivacaine, lidocaine, and triamcinolone injections in conjunction with pelvic floor physical therapy has shown to decrease pain in female patients [26]. These therapies result in decreased pelvic floor muscle tension, thus improving pain [15].

Local Treatments

Local Estrogen Estrogen replacement renders the vagina a more acidic environment to reduce incidence of UTIs. It even allows urothelial healing to improve the efficacy of the mucosal barrier [8].

Urethral Instillations Histopathological examinations of biopsies from women with UPS show inflammatory changes in the urethral mucosa and the paraurethral glands [23]. Women may benefit from anti-inflammatory medications applied directly to the urethra. Lindstrom et al. published a retrospective pilot study of 30 patients who underwent instillation of 2 mL 0.05% clobetasol cream + 2 mL lidocaine gel (unknown strength) intraurethrally. The patients had an average of 4.9 instillations.

There was a 60% rate of relief reported by the patients in the study and at 6 months 56.7% were symptom free. Of their study, 92.9% group would consider the clobetasol + lidocaine for retreatment in the event of a relapse. The basis of the treatment plan was from the idea that inflammation is the cause of the pain [23]. Cooling local anesthetic to 4 °C has been demonstrated to decrease urethral pain in male patients during instillation although there has been a conflicting report of efficacy [27, 28]. This may offer a promising temporary relief to the female patient with UPS.

Systemic Treatments

Antibiotics Many patients have a past history of UTIs and the pathophysiology of UPS may be due to low undetected bacterial counts, or the proliferation of fastidious organisms or commensals that become pathogenic. Antibiotics should only be used in culture proven cases. Antibiotics should not be the first line of therapy in UPS.

Analgesics NSAIDs and other anti-inflammatories are commonly used to control pain. Opioids are not recommended for the treatment of UPS [11].

Alpha-Blockers and Muscle Relaxants Muscle relaxants may help with pelvic floor/sphincter spasms if this is the cause of pain. Alpha-blockers help to decrease bladder neck tone [8, 9]. Reducing spasticity in the urethra will alleviate signs and symptoms of UPS. Alpha-blockers act by relieving increased muscle tone at the bladder neck and the proximal urethra. Commonly used alpha-blockers include doxazosin, terazosin, and tamsulosin. Propiverine hydrochloride contains calcium-blockade properties and has also been used for urethral muscle relaxation. [16]

Anticholinergics and Beta-3 Agonist Anticholinergic medications are used to relieve urinary frequency and urgency. They are not meant to treat dysuria. They act by decreasing detrusor contractility, thus relieving bladder-related symptoms.

Beta-3 receptors have been found to contribute to urethral smooth muscle relaxation. Mirabegron is the first beta-3 agonist that is approved for the treatment of overactive bladder syndrome. In 2015, a study investigated the effect of Mirabegron in mouse urethra. The result was that this drug produced concentration-dependent urethral smooth muscle relaxation due to its selective alpha-1 blockade and beta-3 agonist activity. The use of beta-3 agonists in mice urethra was shown to decrease bladder outlet resistance and perhaps decrease turbulent urine flow [29].

Anxiolytics and Antidepressants Anxiolytics and antidepressants have shown to play a crucial role in therapy. SSRIs are used for their antidepressant properties, while tricyclic

antidepressants are beneficial for not only improving mood but also for decreasing chronic pain. Caciki et al. from Turkey treated 31 male patients with UPS with sertraline and gabapentin. The starting doses of sertraline 50 mg and gabapentin 300 mg were administered once daily. They titrated the medication up to 600 mg gabapentin/day and 100–200 mg sertraline/day depending on each patient's response. They reported on 6-month outcome based on HAM-A, VAS, IPSS, and QoL questionnaires. All patients reported improvement in their UPS at 6 months. The study, however, is limited by the short duration of follow up of 6 months [5].

Psychological Support

Due to the frustrating nature of the disease, supportive psychotherapy is an integral component of management. Patients should be regularly be followed-up and also provided with education, encouragement, and reassurance. Adequate support and counseling may even decrease the need for antidepressants and anxiolytics.

Other Treatments

Urethral Dilatation A large study of 500 female patients with UPS was conducted over a 2-year period and found that two-thirds of the subjects had improvement of symptoms with urethral dilation to 26 to 28 F. Ultimately, however, the study concluded “there currently exists no justification” for use of urethral dilation as a treatment modality. Common complications of urethral dilation include infection, urethral perforation, bleeding, and pain. Women who undergo repetitive urethral dilation may suffer from more significant complications like the development of female urethral stricture disease [19]. Thus, with other treatment options available, the risks of urethral dilation outweigh the benefits. Anecdotally, these patients tend to obtain relief immediately after dilation; this may be due to a response similar to the concept of hydrodistention in interstitial cystitis. The mechanical distention disrupts nerve supply and mucosa, leading to regeneration of mucosa. However, we find that symptoms recur with time.

Laser and Acupuncture Other treatment modalities such as ablation of metaplastic urothelium in the trigone with laser has been suggested to help with pain [30]. Traditional Chinese Medicine such as acupuncture and moxibustion, a practice of burning herbs close to the site of pain, has also been used to treat UPS with reports of success [31].

Potassium Citrate/Sodium Bicarbonate Alkalinization of urine with sodium bicarbonate, sodium citrate, or potassium citrate for symptomatic treatment of dysuria has conflicting information. It has not been shown to be effective in patients after cystoscopy to decrease dysuria [32]. It has, however,

demonstrated some symptomatic relief of dysuria in patients with urinary tract infections and bladder pain syndrome [33, 34].

Interstitial Cystitis Treatment While UPS is separate from interstitial cystitis (IC), patients may have overlapping symptoms. Intravesical treatments with DMSO, cystoscopy with hydrodistention, neuromodulation, and intradetrusor botox injections are within the guidelines of treating IC. The risks and benefits of the treatments should be discussed with the patient and could possibly decrease symptoms [16]. Palleschi et al. described replenishing the glycosaminoglycan layer with Hylauril decreases symptoms in patients with UPS [35].

Remission

It is difficult to assess what the remission rate of UPS is after initiation of treatment. Patients may not return for follow up if they feel better or they have sought treatment elsewhere.

Summary of Treatment Approach

1. Counsel patients on different therapies and set expectations.
2. Initiate behavioral modifications with stress reduction and food/diet modifications.
3. Treat the pelvic floor with pelvic floor physical therapy, trigger point and botulinum toxin injections
4. Local treatment with estrogen therapy for postmenopausal females and urethral instillation can be offered to patients.
5. Target pharmacotherapy based on most bothersome symptom with alpha-blockers, beta 3 agonists, anticholinergics, and antidepressant/antipsychotics.
6. Refer to psychiatry for depression/anxiety symptoms, counseling, and support.
7. Surgical options such as cystoscopy with hydrodistention, neuromodulation, and intradetrusor botulinum injection should be offered to patients with bladder-related symptoms.
8. Chronic antibiotics, opioids, and urethral dilation are not recommended in the treatment of UPS.

Conclusion

UPS can be a multifactorial and challenging diagnosis of exclusion and requires individualized, multimodal therapy. Patients often present in frustration after years of seeking treatment and having undergone many tests. It is important to rule out serious diagnoses and take a stepwise approach to treatment. It is pertinent to set expectations with the patient prior to initiation of therapies and keep a close follow up with

management of expectations. When appropriate, patients should be evaluated by psychiatry for support and treatment of concomitant depression and/or anxiety.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Dogweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, et al. A standard for terminology in chronic pelvic pain syndromes: a report from the chronic pelvic pain working group of the international continence society. *Neurourol Urodyn.* 2017;36(4):984–1008 **Defines how to evaluate and diagnose patients with pelvic pain syndromes.**
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology.* 2003;61(1):37–49.
3. Gallagher D, Montgomerie J, North J. Acute infections of the urinary tract and the urethral syndrome in general practice. *Br Med J.* 1965;1:622–6.
4. Zufall R. Treatment of the urethral syndrome in women. *JAMA.* 1963;184:894–5.
5. Cakici OU, Hamidi N, Urer E, Okulu E, Kayigil O. Efficacy of sertraline and gabapentin in the treatment of urethral pain syndrome: retrospective results of a single institutional cohort. *Cent Eur J Urol.* 2018;71(1):78–83.
6. Stamm WE, Wagner KF, Amsel R, Alexander ER, Turck M, Counts GW, et al. Causes of the acute urethral syndrome in women. *N Engl J Med.* 1980;303(8):409–15.
7. Brumfitt W, Hamilton-Miller JM, Gillespie WA. The mysterious ‘urethral syndrome’. *BMJ.* 1991;303(6804):719–20.
8. Phillip H, Okewole I, Chilaka V. Enigma of urethral pain syndrome: why are there so many ascribed etiologies and therapeutic approaches? *Int J Urol.* 2014;21(6):544–8.
9. Fiander N. Painful bladder syndrome and interstitial cystitis: treatment options. *Br J Nurs.* 2013;22(9):S20–7.
10. Clemens JQ, Stephens-Shields A, Naliboff BD, Lai HH, Rodriguez L, Krieger JN, et al. Network MR: correlates of health care seeking activities in patients with urological chronic pelvic pain syndromes: findings from the MAPP cohort. *J Urol.* 2018;200(1):136–40 **Addresses the impact of pain syndromes on healthcare from the frequency of visits.**
11. Engeler DS, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ, et al. European Association of U: the 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur Urol.* 2013;64(3):431–9.
12. Parsons CL. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. *BJU Int.* 2011;107(3):370–5.
13. Engeler DS, Baranowski AP, Borovicka J, Dinis-Oliveira P, Elneil S, Hughes DJ, Messelink EJ, de Williams AC. Guidelines Associates: A. Cottrell SG: EAU Guidelines on Chronic Pelvic Pain. In: European Association of Urology Guidelines Limited Update March 2016. 2016. **Specifically addresses possible etiologies of urethral pain syndrome and general management strategies.**
14. Kullmann FA, McDonnell BM, Wolf-Johnston AS, Lynn AM, Getchell SE, Ruiz WG, Zabbarova IV, Ikeda Y, Kanai AJ, Roppolo JR, et al. Inflammation and tissue remodeling in the bladder and urethra in feline interstitial cystitis. *Front Syst Neurosci.* 2018;12.
15. Ackerman AL, Lee UJ, Jellison FC, Tan N, Patel M, Raman SS, et al. MRI suggests increased tonicity of the levator ani in women with interstitial cystitis/bladder pain syndrome. *Int Urogynecol J.* 2015;27(1):77–83.
16. Kaur H, Arunkalaivanan A. Urethral pain syndrome and its management. *Obstet Gynecol Surv.* 2007;62(5):348–51.
17. Powell NB, Powell EB, Thomas OC, Queng JT, McGovern JP. Allergy of the lower urinary tract. *J Urol.* 1972;107(4):631–4.
18. Krisiloff M. A dietary cure for prostatitis and the urethral syndrome. *Infect Dis Clin Pract.* 2002;11(3):107–10.
19. Bazi T, Abou-Ghannam G, Khauli R. Female urethral dilation. *Int Urogynecol J.* 2013;24(9):1435–44.
20. Spilotros M, Malde S, Solomon E, Grewal M, Mukhtar BM, Pakzad M, et al. Female urethral stricture: a contemporary series. *World J Urol.* 2017;35(6):991–5.
21. Yoon SM, Jung JK, Lee SB, Lee T. Treatment of female urethral syndrome refractory to antibiotics. *Yonsei Med J.* 2002;43(5):644–51.
22. Daley GM, Russell DB, Tabrizi SN, McBride J. Mycoplasma genitalium: a review. *Int J STD AIDS.* 2014;25(7):475–87.
23. Lindstrom B, Hellberg D, Lindstrom A. Urethral instillations of clobetasol propionate and lidocaine: a promising treatment of urethral pain syndrome. *Clin Exp Obstet Gynecol.* 2016;43(6):803–7.
24. Yang TX, Luo DY, Li H, Wang KJ, Shen H. Is urethrectomy necessary during cystectomy in patients with interstitial cystitis or bladder pain syndrome? *Urology.* 2016;97:73–9.
25. Mirkin Y, Malinina O, Zayceva A. Overactive pelvic floor and urethral pain syndrome. Florence: International Continence Society; 2017. abstract 1012
26. Langford CF, Udvari Nagy S, Ghoniem GM. Levator ani trigger point injections: an underutilized treatment for chronic pelvic pain. *Neurourol Urodyn.* 2007;26(1):59–62.
27. Goel R, Aron M. Cooled lignocaine gel: does it reduce urethral discomfort during instillation? *Int Urol Nephrol.* 2003;35(3):375–7.
28. Bhomi KK, Rizal S, Pradhan M, Rijal A, Bhattachan CL. Pain during rigid cystoscopy: a prospective randomized controlled study comparing the benefit of cooled and room temperature lignocaine gel. *Nepal Med Coll J.* 2011;13(1):55–7.
29. Michel MC. How beta3-adrenoceptor-selective is mirabegron? *Br J Pharmacol.* 2016;173(3):429–30.
30. Costantini E, Zucchi A, Del Zingaro M, Mearini L. Treatment of urethral syndrome: a prospective randomized study with Nd:YAG laser. *Urol Int.* 2006;76(2):134–8.

31. Zheng H, Wang S, Shang J, Chen G, Huang C, Hong H, et al. Study on acupuncture and moxibustion therapy for female urethral syndrome. *J Tradit Chin Med*. 1998;18(2):122–7.
32. Carter PG, Lewis P, Abrams P. Urodynamic morbidity and dysuria prophylaxis. *Br J Urol*. 1991;67(1):40–1.
33. Yaxley J. Alkalinisation of urine in patients with infections of the urinary tract. *Br J Med Med Res*. 2016;13(1):1–4.
34. Ueda T, Yoshida T, Tanoue H, Ito M, Tamaki M, Ito Y, et al. Urine alkalization improves the problems of pain and sleep in hypersensitive bladder syndrome. *Int J Urol*. 2014;21(5):512–7.
35. Palleschi G, Pastore A, Al Salhi Y, Leto A, Fuschi A, Capone L, et al. Efficacy of treatment with Hyaluril in females with urethral syndrome: a prospective analysis comparing naive patients with subjects who experienced previous ineffective treatments. Florence: International Continence Society; 2017. Abstract 291

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.