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Present status and advances in bladder pain syndrome: central sensitisation and the urinary microbiome

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IO and LB instigated the article. IO and RC researched and wrote the article; LB, AD and RF edited the article. All authors approved the final version.

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[Abstract]

Key Content:

- Bladder pain syndrome (BPS) presents as a spectrum of urological symptoms with poorly understood pathophysiology. Bladder mucosal injury secondary to low grade sub-clinical infection is a possible trigger, leading to nociceptive upregulation and subsequently, central sensitisation.
- Brain abnormalities associated with BPS suggest that neuropathological brain alterations exist, which may contribute to the perceived pain.

BPS: central sensitisation and urinary microbiome

- Central sensitisation plays a role in the disease pathophysiology via an augmentation in the responsiveness of the central pain signalling neurons.
- The urinary microbiome is implicated as a trigger for the development and maintenance of BPS.
- Future directions to improve treatment strategies include stratification of patients with BPS into subtypes such as peripheral or central disease and investigation of the urinary microbiome and bladder barrier replacement.

Learning objectives

- To update clinicians' knowledge of current research into the urinary microbiome and pain sensitisation in BPS pathophysiology.
- To understand the biodiversity and abundance of urinary microbes and the role of peripheral and central pain sensitisation, which will help identify future management techniques for BPS.

Ethical issues:

- What are the consequences of long-term antibiotics use for BPS management on bacterial resistance?

[Heading 1] Bladder pain syndrome as a chronic pain state

BPS: central sensitisation and urinary microbiome

Though unpleasant, pain is an important facet for survival, forewarning the body of potential (based on a memory of previous pain experience) or actual tissue harm. Pain sensation thus confers protection and is useful for the prevention of further harm.

Tissue injury promotes many adaptations, leading to the recruitment of inflammatory and pain mediators, such as chemokines and cytokines, to the site of damage. The role of these recruited mediators is to aid in tissue repair. In addition, they activate sensory afferents at the site of tissue damage thus triggering the development of pain hyperalgesia. Hyperalgesia, also known as hypersensitivity, is an abnormally increased sensitivity to pain: painful stimuli are experienced as more painful than normal. Hyperalgesia helps with the healing process by ensuring that physical contact with the injured area is reduced while tissue repair continues. Primary hyperalgesia, which is pain at the direct site of injury, as well as secondary hyperalgesia in the surrounding tissue, is thus an important part of the body's defence mechanism. These changes are usually temporary. Abnormal persistence of these adaptations following injury can permit changes that contribute to the development of chronic pain states. The pain itself becomes the primary clinical problem, neither protecting nor supporting tissue healing. Bladder pain syndrome (BPS) is one such chronic pain condition, in which pain is the overriding condition.

BPS, also known as interstitial cystitis (IC), is defined as a spectrum of urological symptoms characterised by persistent or recurrent chronic pelvic pain, pressure or discomfort, which is perceived to be related to the urinary bladder and is accompanied by at least one other urinary symptom, such as urinary urgency or frequency.[1] It is a disease of unknown aetiology, with a poorly understood pathophysiological mechanism. BPS is more common in women than men, with a prevalence rate of 2–

6%.[2] The disease phenotype is varied; some patients display a mild form of the disease and treatment can be undertaken in the outpatient setting, whereas others have a debilitating disease, requiring repeated hospital visits. The treatment objective is therefore focused on restoring function, preventing relapse of symptoms and improving quality of life (Table 1).[2,3] A multidisciplinary approach to management is key to success, where patients are reviewed in dedicated clinics, including specialists in psychology, pain management, urology and urogynaecology.

The mechanisms of pain in BPS are poorly understood. The bladder mucosa is lined by a protective proteoglycan layer. Proteoglycans are large, heavily glycosylated protein moieties, composed of a protein core and glycosaminoglycan (GAG) side chains. They densely cover the luminal surface of the bladder wall, forming a hydrophobic barrier that prevents the permeation of bacteria, proteins and urinary solutes into the underlying muscles and nerves.[4] In the bladder, the intact proteoglycan molecule provides the immediate interface between urine and the bladder wall and is a critical regulator of bladder permeability.[5] This layer may be dysfunctional in some patients with BPS.[6] Pentosan polysulfate sodium (Elmiron®), which has a similar structure to GAGs, is therefore used as a treatment for BPS, as it helps to replace the damaged urothelial barrier in patients with BPS (Table 1).

The precise trigger leading to the development of BPS remains unknown. However, it is possible that bladder injury by irritant chemicals, radiation, blunt trauma, childbirth, infection, urologic instrumentation or surgery, triggers the release of inflammatory mediators, leading to disruption of the protective mucosal proteoglycan barrier.[7,8] Ketamine, a dissociative general anaesthetic that is occasionally abused as a recreational drug, can cause a form of cystitis known as ketamine cystitis. The

symptoms experienced by patients with ketamine cystitis are very similar to BPS. Patients develop pain and bladder ulceration. Recreational use of this drug must be ruled out during assessment of patients presenting with bladder pain.[9] Resident and recruited immune cell proteins, such as chemokines and cytokines, as well as toxic urinary solutes, permeate the damaged mucosal barrier leading to the depolarisation of sensory afferents (Figure 1).[10] These immune cell proteins induce hyperalgesia by increasing the number of nociceptor channels on the afferent nerve surface membrane. Nociceptors are pain signalling neurons, which send signals of actual or potential tissue damage to the spinal cord and brain. They are triggered by chemical, thermal and mechanical stimuli. Their activation by immune cell proteins leads to the peripheral release of neurotransmitters involved in the transmission of pain signals, namely substance P and calcitonin gene-related peptide (CGRP). This is followed by the development of neuropathic pain. The trigger for peripheral and central sensitisation is thus unleashed.

[Heading 1] Central sensitisation and BPS

Since 2000, research into the pathophysiology of BPS had started to investigate beyond the bladder to find other unexploited treatment targets for this syndrome. The role of central sensitisation in BPS was thus further evaluated. Central sensitisation is the “augmentation of responsiveness of central pain-signalling neurons to inputs from low-threshold mechanoreceptors”.[11,12]

Central sensitisation is an umbrella term used to describe a group of disorders sharing common symptoms with no underlying pathology, but with pain being the leading

feature. These conditions are known as central sensitivity syndromes. They include conditions such as fibromyalgia, irritable bowel syndrome (IBS), temporomandibular joint disorder, chronic fatigue syndrome, vulvodynia and headaches.[13] Other pelvic pain symptoms, often thought to be associated with prolapse, especially dragging and vaginal pain, can be caused by central sensitisation.[14] These conditions are mutually associated, with the presence of one syndrome accompanying another.[15] BPS is associated with central sensitivity syndromes such as fibromyalgia, IBS, vulvodynia and migraines: these are a group of medically indistinct syndromes in which central sensitisation plays a significant role.[16]

The increase in central excitability is normally triggered by damage to peripheral tissues and subsequent release of nociceptive mediators such as glutamate, and activation of peripheral nociceptors. Once activated, these low-threshold peripheral nociceptors form synaptic connections with neurons within the central nervous system (CNS) causing pain.[13,17,18] Persistence of the noxious activation, such as a low-grade chronic infection in the bladder, can cause upregulation in the number and activity of peripheral nociceptors, which consequently elicits an increase in the responsiveness of the CNS neurons. Thus, normal sensory inputs such as touch or heat, begin to produce abnormal painful responses, and clinical pain syndromes (such as tactile allodynia and hyperalgesia) are manifest (Figure 2). In BPS, bladder filling, which is normally an innocuous stimulus, causes pain. Although the pain feels like it originates in the periphery, it is a manifestation of abnormal sensory processing within the CNS.

Factors predisposing to central sensitisation are varied. Direct injury to CNS structures secondary to insults such as infection, trauma or ischemia can precipitate central sensitisation. However, the mechanisms by which peripheral injury leads to central

sensitisation are more complex. The patient phenotype and their psychosocial and environmental influences are important.[19] BPS is commonly associated with depression and anxiety.[20,21]

Compared with controls, patients with BPS have a significantly lower pain threshold, with segmental mechanical hyperalgesia thought to be associated with central sensitisation.[22,23] Patients with BPS have significantly increased volumes in several regions of the brain, including the primary somatosensory cortex, compared with controls; this is thought to have a role in increased pain sensitivity.[24] A study by Offiah and colleagues[25] supports this finding; they reported resistance to intravesical lidocaine in BPS patients with more severe bladder pain and other associated central sensitivity syndromes.

Chronic pain neuroimaging studies have demonstrated unique changes in brain anatomy and function. Khavari and Boone[26] reported on structural anatomical and regional areas of abnormality in the CNS of women with BPS compared with controls. These abnormalities relate to aspects of the patients' mood, quality of life and daily functioning and are thought to be involved in chronic pain maintenance.[26]

[Heading 1] Use of central modifying drugs in BPS

Amitriptyline is a tricyclic antidepressant commonly used to treat neuropathic pain. It supresses the re-uptake of noradrenaline and serotonin at presynaptic nerve endings of the central and peripheral nervous system. This leads to sedation caused by an antihistamine reaction in the CNS. It has a rapid onset of analgesic effect at higher doses. Studies have shown that whether used alone or in combination with other

medication, amitriptyline is an alternate management strategy for patients diagnosed with BPS: success rates are reported in 45.5–66.0% of patients.[27,28,29] Use is limited to lower doses (mean dose = 55 mg, range 12.5–150.0 mg) owing to significant side-effects, such as dry mouth and weight gain, noted by 84% of patients at the higher, more effective doses.[28]

Gabapentinoids are both peripheral and centrally acting ligands that lead to blockade of calcium channels. Though not a licenced treatment for BPS, they are occasionally considered in this patient group because of their therapeutic effect on visceral inflammatory and neuropathic pain.[30] There are currently no clinical data evaluating efficacy in BPS. Side effects include suicidal ideation, respiratory depression, withdrawal and dependence.

[Heading 1] Other BPS management approaches focussed on central sensitisation

In cases such as BPS, where central sensitisation is thought to be important in the pain pathophysiology, peripheral approaches to management may prove insufficient, as the root driver of pain remains unaddressed. Central neuromodulation may be more effective for symptom control. Peripheral neuromodulation, including sacral nerve stimulation and posterior tibial nerve stimulation, as well as central neuromodulation techniques are alternate management strategies that may be considered for the management of chronic pain syndromes recalcitrant to conventional peripheral treatment approaches. Studies have shown clinically significant improvements in up to 50% of patients.[2,31]

Heading 2] Peripheral neuromodulation

Peripheral neuromodulation, such as posterior tibial nerve stimulation (PTNS) and sacral nerve stimulation (SNS) can lead to improvement of symptoms in patients with chronic pelvic pain and BPS. Their mechanism of action is poorly understood; however, they primarily work on the peripheral nervous system and do not target central pathways. One proposed mechanism of action is the 'gate control theory of pain'. Stimulation of the peripheral nociceptor with a non-noxious stimulus closes the 'gates' to painful stimuli, therefore blocking ascending pain signals to the central nervous system.[32] Other suggested mechanisms include a reduction of pelvic floor hypertonicity, a reduction of inflammatory chemokine levels and stimulation of spinal opioid pathways.[33]

[Heading 2] Deep brain stimulation

Deep brain stimulation (DBS) is a neurosurgical treatment that involves placing neurostimulators into specific anatomical regions of the brain. Septal and medial forebrain stimulation has analgesic effects in acute and chronic pain patients.[34,35] Peripheral effects of stimulation include analgesia, mild euphoria, feelings of warmth, well-being and relaxation. A significant improvement is seen in urinary incontinence and frequency in Parkinson's disease patients following DBS of the subthalamic nuclei in both men and women.[36] DBS has yet to be used specifically for the management of BPS, but the results of these studies are encouraging.

[Heading 2] Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (r-TMS) is a non-invasive therapy that uses magnets to induce a transient electrical current in the cortex underlying the magnetic coil. It works by depolarisation of the surrounding cortical neurones, resulting in a reorganisation of pathological neuronal networks. A randomised, double-blinded, sham-controlled study to investigate the use of r-TMS in treating BPS was performed.[37] In this study, patients with pharmacological treatment-resistant BPS underwent cyclical treatment of either real r-TMS or sham r-TMS (placebo). They showed a significant reduction in pain score following real r-TMS compared to sham. Also noted was an improvement in lower urinary tract symptoms, most notably bladder emptying, and an improvement in quality of life. This study, as well as a case report by Nizard and colleagues,[38] which describes improvement of BPS symptoms in a woman following high-intensity, low-frequency r-TMS of the pre-frontal cortices, demonstrates the positive effects of central pain modulation in patients with centralised BPS phenotypes.

[Heading 1] Urinary microbiome

Until recently, urine was considered sterile in the healthy subject and the presence of bacteria in the urine was associated with a urinary tract infection (UTI). However, in the early 2010s, use of high-throughput molecular DNA sequencing of bacterial 16S rRNA genes enabled the analysis of complex microbial communities inhabiting the human urinary tract.[39,40] It is now widely accepted that the bladder has a healthy bacterial flora: the urinary microbiome.

BPS: central sensitisation and urinary microbiome

Microbiome is a term used to define the combined community of commensal, symbiotic and pathogenic microorganisms that exist throughout the human body. Each body site has a specific microbiota, dependent on the individuals' habits, geographical location and genetic make-up. The microbiome can be vital in maintaining health, but when it becomes disrupted it enters a state of 'dysbiosis,' which may contribute to disease. An imbalance of the gastrointestinal tract microbiota, for example, has been associated with inflammatory bowel disease, asthma and obesity. It is therefore plausible that dysbiosis in the bladder microbiome could be responsible for chronic disease states. Studies detailing the composition of the urinary microbiome and linking the healthy urinary microbiome with health, and urinary dysbiosis with disease, are therefore attracting much interest but are still in their infancy.

The urinary microbiome alters in response to various factors, such as health and disease, as well as menopausal status.[41] In healthy females, the most abundant genera of bacteria found in the bladder include *Lactobacillus, Prevotella, Streptococcus* and *Gardnerella*.[41,42] To further explore the role of infection in BPS, Warren and colleagues[43] investigated urine samples of women within a year of the onset of BPS diagnosis. They found that bacteriuria was present at the onset of BPS in some women, hinting at a possible disease pathogenesis.

[Heading 1] Use of antibiotics in the management of BPS: success or failure?

Secondary to this alteration in the urinary microbiome, there has been a refocus on the use of long-term, low-dose antibiotics for the management of BPS and its associated lower urinary tract symptoms (LUTS).

BPS: central sensitisation and urinary microbiome

At first, studies into the use of antibiotics for BPS management appeared discouraging. A randomised, double-blind, placebo-controlled trial of antibiotics in patients with BPS reported a nonsignificant overall improvement in pain and urgency symptoms following antibiotic treatment compared with placebo.[44] Antibiotics used in this study were rifampicin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin and ciprofloxacin for 3 weeks each. These findings were echoed by a more recent study, which reported no improvement in questionnaire scores following treatment of bacteriuria with a regime of 3–5 days of either nitrofurantoin, trimethoprim or fluoroquinolone in BPS patients.[45] The results did, however, show a nonsignificant decrease in visual analogue scores (VAS) for pain following antibiotic treatment. These studies suggest that neither a long nor short course of antibiotics is a major advance in the management of BPS as their use does not lead to a resolution of pain or LUTS.

Further studies have demonstrated a reduction in bacterial culture levels and improvement in BPS LUTS following treatment with antibiotics (Table 2).[46–50] These studies suggest that use of low-dose, long-term antibiotics leads to symptom improvement and are a possible treatment strategy for the management of patients with chronic BPS pain and LUTS. However, none of these are randomised or level one studies. The studies have differing study populations, methods of BPS diagnosis, assessment of improvement and questionnaires used. In addition, no comparison of the efficacy of antibiotic treatment has been made with other established treatments for BPS. If considering antibiotic use for BPS management, it is prudent to pay attention to reported side effects and to consider an alternate antibiotic, duration of use, dosage and treatment regimen. Implications for antibiotic resistance should also be considered.

BPS: central sensitisation and urinary microbiome

These most recent papers on antibiotic success in BPS have been published since the release of the Royal College of Obstetricians and Gynaecologists' 2016 Green-top guideline on 'Management of bladder pain syndrome'. This guideline states that "long-term antibiotics … are not recommended for BPS."[2] The effect of antibiotics on this complex syndrome deserves further research, as a review of the evidence seems to indicate that antibiotics might indeed have a role to play in disease management.

[Heading 1] Future directions

Research into BPS over the last 30 years has resulted in a new understanding of the bladder urothelium and the impact of urothelial injury on the symptoms experienced by patients with BPS. Research continues into discovering new biomarkers to better subtype patients. The stratification of patients into BPS subtypes is important to determine the treatment modalities or targets that would be most effective. Several novel therapies have shown promise in small clinical trials. These include monoclonal antibodies, which target the overexpression of immune-mediated cytokines, and cannabinoids, frequently successfully used in other chronic pain conditions.[51] iAluRil®, which contains hyaluronic acid and chondroitin sulfate, has shown efficacy in the management of recurrent UTIs. In a cohort study of 157 patients with recurrent UTIs,[52] a course of four instillations over four consecutive weeks, followed by monthly instillations for 5 months led to a significant reduction in UTI frequency and improvement in patient symptoms and quality of life. By replenishing the GAG layer, this medication – already in use for BPS patients – may protect the underlying sensory nerves and prevent the onset or break the cycle of central sensitisation in patients with BPS. Future research is needed to examine this hypothesis.

[Heading 1] Conclusion

Bladder pain syndrome is a complex pain condition, which probably involves malfunctions of both the peripheral and central nervous systems. Treatment is aimed at improving quality of life and preventing relapse. A multimodal approach to treatment, involving lifestyle modification and pharmacological therapy targeting both the bladder peripherally and the CNS, is recommended. Low-dose, long-term antibiotic therapy may be effective after treatment failure with other agents in alleviating symptoms. A multidisciplinary approach to management is key to success.

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No conflicts of interest to disclose.

[Heading 1] Figure legends

Figure 1. Schematic of barrier disruption in BPS. In an intact bladder, the proteoglycan molecules and their attached glycosaminoglycans (GAGs) form a hydrophobic layer, thus preventing the permeation of urinary solutes to the underlying epithelial cells; the afferent fibres remain protected. Damage to the proteoglycan molecules through deglycosylation of the GAG side chains or complete proteoglycan loss leads to an ineffective barrier. Toxic urinary solutes pass through the normally impermeable barrier depolarising the underlying nerve. K^+ = potassium.

Figure 2. Central sensitisation. The normal pain response curve is shifted to the left with central sensitisation. As a consequence, typically innocuous stimuli are deemed painful (allodynia) and noxious stimuli are more painful (hyperalgesia). These are two of the main features of central sensitisation. VAS = Visual analogue scale: numerical 11-point pain scale from 0, which denotes maximal pain threshold.

[Heading 1] Tables

Table 1. Management of bladder pain syndrome (BPS). A combination of conservative management with behavioural modification and physical therapy alongside pharmacotherapy is crucial for the successful management of BPS.

Approach	**Treatment/ course of action**	**Rationale**		
Lifestyle modification	Dietary modification	Avoid caffeinated beverages, alcohol, citrus fruits and juices, spicy foods, tomatoes, carbonated drinks, chocolate, as these are irritants to the bladder		
	Avoid constipation	Can worsen bladder symptoms		
	Smoking cessation	Nicotine is a bladder irritant		
	Avoidance of UTI	Increase water intake as concentrated urine can irritate the bladder		
	Bladder training	Avoid frequent micturition 'just in case' to prevent bladder shrinkage		
Oral therapies	**Treatment**	**Method of action**	**Effect on bladder**	**Side effects**

	Elmiron® (pentosan polysulphate)	Replacement of urothelial barrier	Analgesic effect	Retinal pigmentation
	Anticholinergics	Increased bladder capacity and reduced detrusor contractions	Controls frequency, urgency and urgency urinary incontinence	Dry eyes, dry mouth, constipation
	Analgesia: Amitriptyline	Tricyclic antidepressant	Bladder relaxation at low doses, analgesic with higher doses	Nausea, blurred vision, skin rash and constipation or diarrhoea
	Antibiotics	Low-dose long-term antibiotic use may lead to symptoms improvement		
Intravesical medication	Cystistat®	Bladder mucosal GAG replacement therapy providing analgesic effect		
	iAluRil®	Bladder mucosal GAG replacement therapy providing analgesic effect		

	Intravesical botulinum toxin A	Botulinum toxin bladder injections inhibits acetylcholine release resulting in temporary flaccid muscle paralysis
Bladder distention	Cystoscopy and hydrodistention	Allows confirmation of diagnosis Low-pressure hydrodistention provides relief of frequency and urgency
Neuromodulation	Posterior tibial nerve stimulation	Fine needle electrode is inserted at the ankle to stimulate the tibial nerve Weekly sessions for an average of 12 weeks is required
	Sacral nerve stimulation	Implanted nerve device for stimulation of the sacral nerve Used for the treatment of severe urgency, frequency, and urinary retention

Further detailed guidance can be obtained from the AUA and RCOG Guideline[2,3]. GAG = glycosaminoglycans; UTI = urinary tract infection

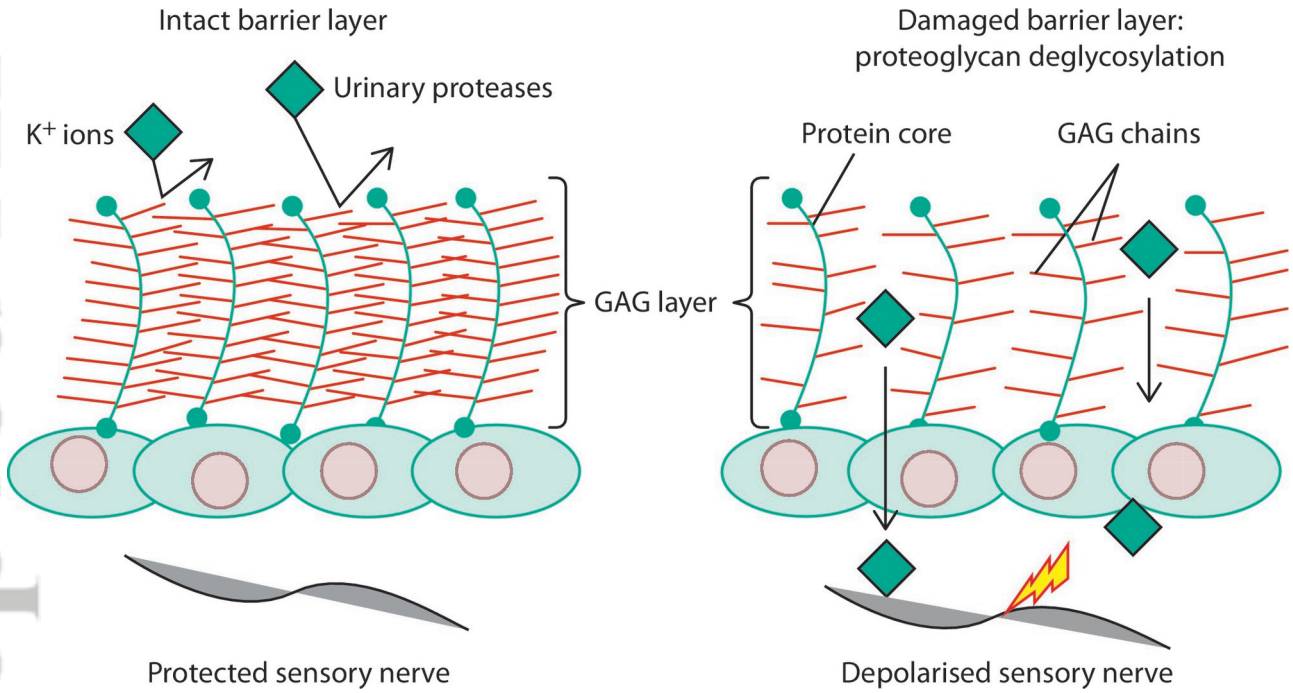
Table 2. Studies detailing results of antibiotic treatment response in patients with BPS or painful LUTS. Treatment led to resolution of symptoms.

Author; year	**Study type**	**Patients; number**	**Antibiotic treatment**	**Assessment questionnaires**	**Findings**
Zhang; 2009[44]	Cross-sectional	IC/BPS; n = 27	Tetracycline: intravesical and oral x 3 months	O'Learly Sant symptom and problem index; Pain, urgency and frequency symptom scale.	Reduction in nano-bacterial levels with associated reduction in severity of symptoms
Nickel; 2014[45]	Cross-sectional	BPS; n = 93	Not specified	IC symptom and problem index; Pain, urgency and frequency symptom scale; Visual analogue scale of pain, frequency and urgency: 0–10.	Individualised phenotype directed treatment, including antibiotics for bacteriuria, demonstrated a significant clinical improvement in symptoms

Swarmy ; 2018[46]	Case series	Chronic LUTS and pyuria including IC/BPS; n = 624	Nitrofurantoin, trimethoprim and cefalexin x 14 days, repeated for 12 weeks until no symptomatic deterioration after antibiotic withdrawal	Patient global impression of improvement scale	Reduction in LUTS, 24-hour frequency, urinary urgency, lower urinary tract pain, voiding symptoms and pyuria.
Aydogan; 2019[47]	Case series	IC/BPS; n = 26	Oral fluoroquinolones or cefuroxime	O'Leary Sant symptom and problem index	Reduction in median symptom and problem index scores

Swarmy ; 2019[48]	Cross sectional	Painful LUTS and microscopic pyuria; n = 1035: 221 had unplanned treatment cessation	Cefalexin, trimethoprim and nitrofurantoin: until optimal symptom control	Symptom score[50]	90% of patients with unplanned discontinuation of long-term antibiotic treatment reported a flare of LUTS and deterioration in symptoms This was followed by recovery with re-instatement

BPS = bladder pain syndrome; IC = interstitial cystitis; LUTS = lower urinary tract symptoms;



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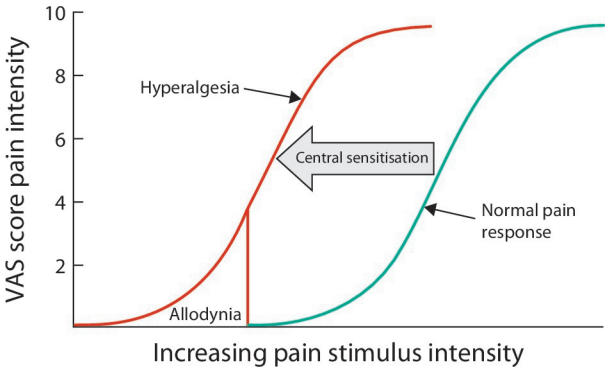

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