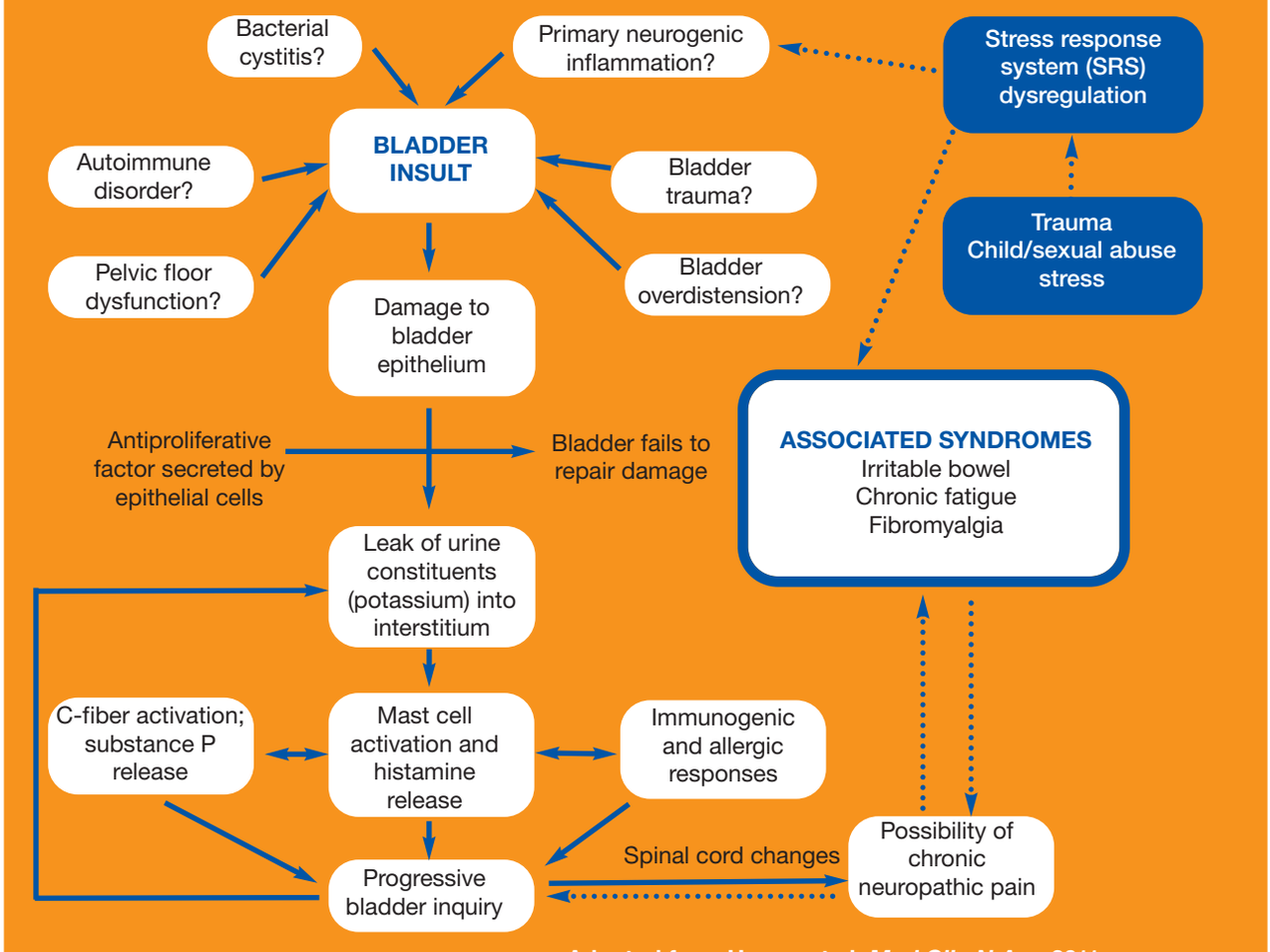
Bladder pain syndrome/interstitial cystitis:
Current therapeutic perspectives

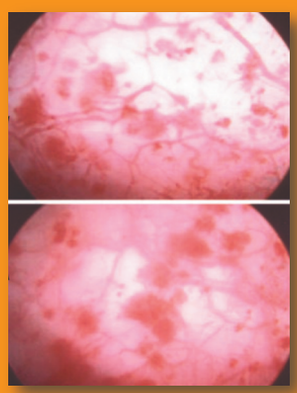
Paulo Dinis
MD, PhD
Department of Urology, Faculty of Medicine of Porto, Hospital de S João, Porto, Portugal

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating chronic disease of unknown etiology characterized by pain, pressure or discomfort perceived to be related to the bladder, accompanied by at least one other urinary symptom. Confusable diseases must be excluded. The presence of other organ symptoms as well as cognitive, behavioral, emotional and sexual symptoms, should be addressed.[1] The case for BPS/IC as being part of a larger functional systemic disorder is increasingly supported by the fact that BPS patients often present with varying non-bladder syndromes, namely irritable bowel syndrome, fibromyalgia, vulvodynia, chronic fatigue syndrome, migraine,

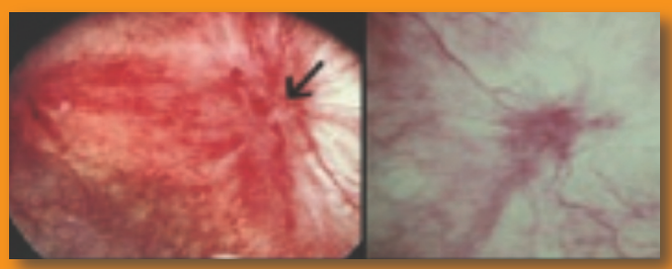
FIGURE 1 Bladder pain-syndrome (BPS) – pathophysiology



Adapted from Hanno et al. *Med Clin N Am,* 2011



Glomerulations
Johansson et Fall, *J Urol* 1990



Hunner's lesion (arrow)
Marinkovic et al, *BMJ* 1990

FIGURE 2 Bladder cystoscopic findings in BPS

panic disorder and social anxiety disorder.[2,3] Furthermore epidemiological studies have shown a high prevalence of child abuse, sexual and other, in BPS/IC patients.[4] Various studies have shown high urinary and plasma adrenaline levels and functional alteration of sympathetic autonomic function.[5] Patients with IC present with increased heart rate at baseline and throughout mental stress challenge in laboratory studies and have increased startle reflex.[6,7] They also have significant increase of symptoms with daily stressors.[8] Experimental studies in murine models have shown that sustained epinephrine administration induces bladder wall alterations similar to those found in BPS/IC patients.[5] Taken together these data point even more to the possibility that BPS/IC or part of

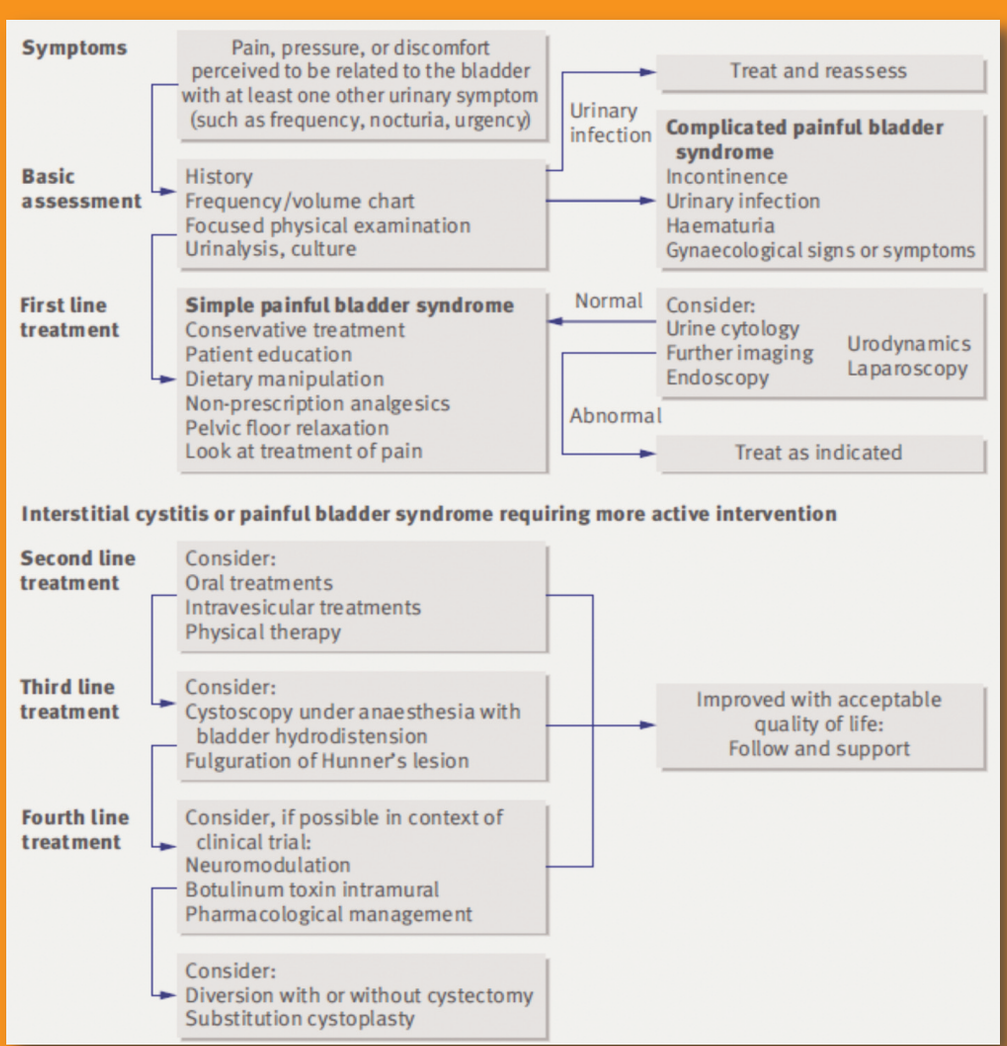
FIGURE 3 Treatment algorithm for BPS

What patients are like is important:

- Depression
- Anxiety
- Panic attacks
- Catastrophizing
- Functional systemic non-bladder syndromes (FSS)

What patients eat is important:

- Coffee, tea,
- Soda,
- Alcoholic beverages,
- Citrus fruits and juices,
- Artificial sweeteners,
- Hot pepper



Adapted from Marinkovic et al, *BMJ* 2009

it might be an aspect of a broader systemic disease where the stress response system (SRS) alteration, plays an important role (Figure 1). Despite this, most research up to now has centered on the bladder as the site of a putative initial insult that triggers a reaction whereby bladder epithelium would become leaky. This would lead to an inflammatory process in the bladder wall, generating inflammation and pain (Figure 2). Eventually, in prone individuals, neuroplasticity of pain circuits would lead to chronic pain. Treatment is not well defined and is still under intense investigation. Most patients are initially controlled with general measures: counselling, avoidance of some comestibles (caffeine, alcohol, chocolate, tea, spicy food), stress alleviating activities and over the counter analgesics on demand. Mainstays of oral therapies are empirical due to lack of knowledge on etiology of this disease. The few oral drugs that showed efficacy in placebo controlled trials are amitriptyline, pentosan polysulfate sodium, hydroxyzine and cyclosporine A (Figure 3 and Table 1). As for intravesical treatments reasonable evidence is available for dimethyl sulfoxide (Table 2) and resection of visible Hunner's lesions. Neuromodulation and reconstructive surgery can also be recommended in selected cases (Table 3). Further studies into the causes and mechanisms of the disease are paramount for the development of effective treatments. Foreseeable therapeutic objectives will likely include oral blockade of sensory nerve receptors, immune system modulation, peripheral nerve fiber inactivation/desensitization, anti-proliferative factor blockade and pain gene therapy.[9] However, identification of BPS/IC phenotypic subgroups

Table 1 BPS oral treatments

Treatment	LE	GR	Comment
Analgesics	2b	C	Indications limited to cases awaiting further treatment
Corticosteroids	3	C	Corticosteroids not recommended as long-term treatment
Hydroxyzine	1b	A	Standard treatment, even though limited efficacy shown in RCT
Cimentidine	1b	B	Insufficient data
Amitriptyline	1b	A	Standard treatment
Sodium pentosanpolysulphate	1a	A	Standard treatment. Data contradictory
Antibiotics	1b	A	Limited role in the treatment of IC
Prostaglandins	3	C	Insufficient data on IC, adverse effects
L-arginine	1b	C	Effect in IC uncertain
Cyclosporin	1b	A	RCT: superior to PPS but more adverse effects
Duloxetin	2b	C	No effect, tolerability poor
Oxybutynin/tolterodine	3	C	Limited indication in IC
Gabapentin	3	C	Preliminary data so far
Suplatast tosilate	3	C	Preliminary data so far
Quercetin	3	C	Preliminary data so far

Table 2 BPS intravesical treatments

Treatment	LE	GR	Comment
Intravesical anaesthesia	3	C	
Intravesical PPS	1b	A	
Intravesical heparin	3	C	
Intravesical hyaluronic acid	2b	B	
Intravesical chondroitin sulphate	2b	B	
Intravesical DMSO	1b	A	
Intravesical Bacillus Calmette Guerin	1b	Not recommended	
Intravesical clorpactin	3	Not recommended	Obsolete
Intravesical vanilloids	1b	C	Data contradictory

LE = level of evidence: GR = grade of recommendation

Tables 1 and 2: Fall M, Baranowski AP, Elneil S, et al. *Eur Urol* 2010

Table 3 BPS interventional procedures

BPS interventional treatments

- Hydrodistension
- Neuromodulation
- Transurethral resection of Hunner's lesion
- Major surgery

Procedure	LE	Recommendation
Hydrodistension	3	C
Ulcer resection, fulguration	3	C
Cystolysis	3	-A (not recommended)
Sympathetic deinervation	3	-A (not recommended)
Parasympathetic deinervation	4	-A (not recommended)
Cystoplasty	3	C
Urinary diversion ± cystectomy	3	C

Hanno P, Lin A, Nordling, et al. *Neurourol Urodvn* 2010

should help delineate individualized treatment which will be aimed at the disease and its multiple manifestations rather than at bladder focused complaints. Patient classification can rely on subtyping (eg, according to International Society for the Study of BPS criteria) and or be based on clinical criteria such as forwarded by Nickel et al.[10] In the latter classification, Urinary, Psychological, Organ specific, Infection, Neurological/systemic disorders and Tenderness in muscles (UPOINT)[10] domains are evaluated and approached in an integrated manner (Figure 4). This means that complaints not bladder related but equally damaging to patient well being are systematically sought and classified and patients treated for the entire clinical picture they present with. Stemming from UPOINT phenotyping, the future will see evaluation and treatment of BPS/IC become increasingly multidisciplinary. Co-existing bladder diseases like infection or others causing lower urinary tract symptoms, non-bladder syndromes, as well abuse/traumatic events will be systematically evaluated. Treatment will evolve from an organ (bladder) centered approach to a new paradigm where psychological and psychiatric support, physical therapy, management of infection, and the treatment of non-bladder regional and distant pain complaints will be readily available to the BPS/IC patient along with the traditional end organ approach.

FIGURE 4 BPS clinical phenotyping and comprehensive multidisciplinary treatment

Urinary Urgency Frequency Dysuria	U
Psychosocial Depression Maladaptive coping mechanisms Social interaction problems	P
Organ specific Pain with bladder cycle Glomerulations/Hunners' ulcers Inflammation in biopsy specimen	O
Infection Significant bacteriuria that worsens symptoms and improves with antibiotic treatment	I
Neurologic/systemic conditions Irritable bowel syndrome Fibromyalgia Chronic fatigue syndrome Vulvodynia Any other condition that suggested neuropathy or neural upregulation	N
Tenderness of skeletal muscles Tenderness or pain in pelvic or abdominal muscles and ligaments	T

Adapted from Nickels et al, *J Urol* 2009; 182: 155–160

References

1 van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol* 2008; 53: 60–67.

2 Warren JW, Morozov V, Howard FM. Could chronic pelvic pain be a functional somatic syndrome? *Am J Obstet Gynecol* 2011; 205: 199 e1–5.

3 Talati A, Ponniah K, Strug LJ, Hodge SE, Fyer AJ, Weissman MM. Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. *Biol Psychiatry* 2008; 63: 594–601.

4 Mayson BE, Teichman JM. The relationship between sexual abuse and interstitial cystitis/painful bladder syndrome. *Curr Urol Rep* 2009; 10: 441–447.

5 Charrua A, Pinto R, Taylor A, Canelas A, Ribeiro-da-Silva A, Cruz CD, et al. Can the adrenergic system be implicated in the pathophysiology of bladder pain syndrome/interstitial cystitis? A clinical and experimental study. *Neurourol Urodyn* 2013 Dec 24.

6 Lutgendorf SK, Latini JM, Rothrock N, Zimmerman MB, Kreder KJ, Jr. Autonomic response to stress in interstitial cystitis. *J Urol* 2004;1 72: 227–231.

7 Twiss C, Kilpatrick L, Craske M, Buffington CA, Ornitz E, Rodriguez LV, et al. Increased startle responses in interstitial cystitis: evidence for central hyperresponsiveness to visceral related threat. *J Urol* 2009; 181: 2127–2133.

8 Rothrock NE, Lutgendorf SK, Kreder KJ, Ratliff TL, Zimmerman B. Daily stress and symptom exacerbation in interstitial cystitis patients. *Urology* 2001; 57 (6 Suppl 1): 122.

9 Diniz S, Dinis P, Cruz F, Pinto R. Bladder pain syndrome/interstitial cystitis: present and future treatment perspectives. *Minerva Urol Nefrol* 2013; 65: 263–276.

10 Nickel JC, Shoskes D, Irvine-Bird K. Clinical phenotyping of women with interstitial cystitis/painful bladder syndrome: a key to classification and potentially improved management. *J Urol* 2009; 182: 155–160.