REVIEW ARTICLE

Drugs 2009; 69 (3): 279-296
0012-6667/09/0003-0279/$55.55/0

Paediatric Painful Bladder Syndrome/ Interstitial Cystitis

Diagnosis and Treatment

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Abstract

To describe the pathophysiology, diagnosis and controversies surrounding the diagnosis and pharmacological treatments of painful bladder syndrome/ interstitial cystitis (PBS/IC) in children, we reviewed adult and paediatric literature pertaining to PBS/IC.

Paediatric PBS/IC presents similarly to adult PBS/IC. The diagnosis is made by exclusion. Paediatric PBS/IC patients complain most commonly of urinary frequency, and abdominal pain occurs in up to 88% of affected children. Enuresis may also be a presenting complaint. Urinalysis and urine cultures are unremarkable. Management of paediatric PBS/IC is similar to that of adult PBS/IC, and non-surgical management includes dietary, lifestyle and pharmacological therapy. Pharmacological options include pentosan polysulfate, amitriptyline, hydroxyzine, cimetidine or intravesical therapies (dimethyl sulfoxide or 'therapeutic solution').

Painful bladder syndrome/interstitial cystitis (PBS/IC) is characterized clinically as urinary urgency, frequency, nocturia and/or pelvic pain.[1] There is no specific confirmatory diagnostic or pathology test for PBS/IC, making PBS/IC a clinical diagnosis.[2] As a result, the true prevalence

of PBS/IC is debated, based on how the syndrome and diagnostic criteria are defined.[3] Traditionally, urologists used strict criteria of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to diagnose PBS/IC, which largely mandates moderate to severe symptoms and excludes from diagnosis any patient with any of a list of alternative diagnoses that might serve as confounding factors (bacterial cystitis within the last 3 months, active genital herpes, distal ureteral or bladder stone, vaginitis, unstable detrusor contractions, schistosomiasis, bladder tuberculosis). These criteria were defined for research trials to ensure homogeneity of subjects, but were adopted by many clinicians. If NIDDK criteria are used, the diagnosis is missed in at least 60% of patients.[4] Recent prevalence estimates in adults are 52–12 600 per 100 000 women and 8–41 per 100 000 men, or roughly 60 000–15 000 000 adult women and 10 000–50 000 adult men in the US.[5-9] Despite controversies and varying definitions in PBS/IC diagnosis, with some prevalence estimates much higher, it is generally accepted that there are at least 1 million American women diagnosed with the condition, and likely many more undiagnosed.[10,11]

The prevalence of PBS/IC in children is unknown. The NIDDK criteria (from 1988) excluded diagnosing PBS/IC in patients <18 years of age, for no reason other than to avoid the difficulty of obtaining consent from minors for research trials.[3] Older studies suggest that PBS/IC in children presents similarly to that occurring in adults.[12-16] Anecdotal observations of adult patients indicate that approximately 25% of adults with PBS/IC report having chronic urinary tract problems as children or that their symptoms developed when they were children and progressed in severity over time, implying that early diagnosis and treatment might have avoided morbidity.[17]

In this article, we first review the evidence on adult PBS/IC, which is controversial, even among experienced researchers and clinicians. We then review what is known about paediatric PBS/IC. We discuss the diagnosis, evaluation and medical management of PBS/IC, but not surgical management.

1. Painful Bladder Syndrome/Interstitial Cystitis (PBS/IC) in Adults

1.1 Normal Bladder Function

The normal viscoelastic bladder has several properties to allow it to store and empty properly. The bladder fills at a low pressure and maintains a low pressure at capacity (normal compliance). Throughout filling, the normal bladder exhibits no involuntary detrusor contractions. Most healthy adults have no conscious perception of bladder filling until a threshold volume is reached, typically around 80–120 mL, when they first perceive filling. Most individuals ignore this sensation and can continue to perform their daily activities until a capacity of approximately 150–180 mL is reached. If a bathroom is convenient, most people would void at this volume, but in most circumstances, individuals will continue to do their daily activities and allow their bladder to fill to approximately 240–280 mL, when they will stop their activities, and look for a bathroom in which to void.[18] Throughout filling, bladder mechanoreceptors sense stretch and encode action potentials based on various thresholds of stretch.[19] The frequency with which these mechanoreceptors encode and the sequential recruitment of low and high threshold receptors (mostly A-δ fibres) are relayed via pelvic afferent fibres to spinal and supraspinal centres, where the information is processed. Assuming typical urine output of 50–70 mL/h, most individuals void every 4–6 hours during the day. When micturition is desired, the brain releases its inhibition on the sacral micturition centre (S_{2-4}), which enables a coordinated micturition reflex of external sphincter relaxation and detrusor contraction to occur. The bladder empties to completion with normal micturition.

Given the prolonged dwell times during which urine and urinary solute bathes the bladder in the filling phase, the bladder has a mechanism to avoid reabsorption of water and solutes across the urothelium. The bladder is lined by transitional cell epithelium, and on its luminal surface there is a thick, arborized layer of mucin, composed of glycosaminoglycan (GAG), chondroitin

sulphate, hyaluronic acid, dermatan sulphate and free floating mucus. The mucin coating is hydrophilic and acts as an adhesion and permeability barrier.[20,21] Disruption of the mucin coating, even with the transitional cell layer intact, allows for abnormal solute permeability.[22]

1.2 PBS/IC Pathophysiology

The pathophysiology of PBS/IC is controversial. However, we interpret from the preponderance of data that PBS/IC is largely an issue of bladder sensory afferents causing hypersensitivity and allodynia. The majority of patients have epithelial dysfunction, whereby the normal barrier function of the bladder urothelium fails and allows for abnormal epithelial permeability of urinary solutes into the bladder submucosa.[23-25] The initial cause of abnormal epithelial permeability is not known. The initial inciting factor may be varied. In an *in vivo* experiment, mouse bladders were provoked either with bacterial-derived lipopolysaccharide, antigen or substance P.[26] Notwithstanding some differences, there were common genes and proteins expressed regardless of injury. We infer therefore that the bladder has a stereotypical response to multiple types of injury.

Once injury and abnormal epithelial permeability occur, urinary solute, such as potassium, may diffuse across the epithelium and produce smooth muscle injury to the detrusor, provoking an inflammatory response. Furthermore, the solute may directly depolarize sensory nerves and may produce localized pain.[23] This defect in bladder mucin function with potassium-induced sequelae is referred to as the 'GAG theory'. Mast cells are also activated in many PBS/IC patients.[27] Mast cells release histamine, and histamine may induce release of the pain neurotransmitter substance P and induce proliferation of (pain sensing) C fibres.[28,29] In late-phase PBC/IC, increased density of nerve fibres, and in particular of non-myelinated C fibres, is seen.[30-32] The 'GAG theory' ties together data to explain how abnormal epithelial permeability causes the 'leak' of solute into the submucosa, submucosal injury and inflammation, mast cell activation and histamine release, and subsequent neural (pain fibre) activation and recruitment in the bladder, spinal cord and brain (table I).[33]

An alternative theory is that mast cell activation occurs first, and releases histamine that, in turn, produces epithelial dysfunction, propagates more mast cell activation, and results in subsequent release of substance P and neural activation.[35] Some authors cite evidence of primary nerve inflammation.[37] There is increased nerve fibre density and nerve fibre destruction in proximity to mast cells.[36] Moreover, some patients demonstrate central sensitization with limbic dysfunction.[38,39] It is conceivable that central sensitization may occur first, with later development of bladder symptoms.[40,44] Central sensitization helps to explain non-bladder-related symptoms commonly seen in PBS/IC, such as pelvic floor dysfunction, irritable bowel syndrome and vulvodynia.[41] These processes may have a genetic component. In a study of twins, when one twin had IC, the other twin was more likely to have IC if they were monozygotic versus dizygotic twins.[45] Five of eight monozygotic twin pairs thought to have PBS/IC in the study had their urine antiproliferative factor (APF) assayed. All five twin pairs showed abnormal APF activity.

The majority of patients demonstrate increased epithelial permeability, bladder hypersensitivity and allodynia, and increased encoding of bladder sensation from normally quiescent C fibres.[22,23,33,34] IC is characterized by hypersensitivity to both nonpainful and normally painful stimuli. Increased input from sensitized

Table I. Summary of pathophysiological factors in painful bladder syndrome/interstitial cystitis

Factor	Supporting evidence
Bladder epithelial dysfunction	Histology, permeability studies, potassium testing[22-25,34]
Mast cell	Increased mast cells, increased histamine[27-29,35,36]
Neural activation and upregulation	Increased nerve fibre density, proliferation of unmyelinated C fibres, hypothalamic-pituitary-adrenal axis abnormalities[30-33,37-43]

bladder afferents leads to the release of neuroactive chemicals in the spinal cord dorsal horn, which results in central (spinal) hyperexcitability.[33,42] A proposed pathophysiological mechanism is shown in figure 1. Although there are occasional reports citing infection as a factor in the pathophysiology or in the response to antibacterial therapy, the overwhelming majority of studies show no evidence of infection or infectious aetiology.

1.3 Clinical Presentation

Clinically, PBS/IC is characterized by urinary urgency, frequency, nocturia and pelvic pain (table II).[1,40,46,47] The classic patient is diagnosed in their forties, and the diagnosis is 5- to 10-fold more common in females.[6] Pain is variable, and patients localize pain in the suprapubic region, lower quadrants, vagina, urethra, perineum, medial thighs and external genitalia.[46] The radiation of pain is variable. In early-phase disease, patients often have no pain, or describe pressure or discomfort rather than pain.[48,49] Symptoms are often exacerbated or triggered just prior to menses (thought to represent mid-cycle estrogen surge that results in histamine release from mast cells), and by specific foods (often spicy foods, acidic foods, citrus, tomato products, potassium-rich foods, such as bananas, chocolate, carbonated drinks, caffeinated drinks, alcohol), sex and stress.[1,43,50-55] Typically, patients describe increased pain if they try to forestall micturition and relief of pain after voiding.[53] As the disease progresses, pain tends to be less variable and more unremitting.

Because symptoms are nonspecific and similar to other mimicking conditions, patients are often misdiagnosed with recurrent bacterial cystitis, endometriosis, overactive bladder (OAB), chronic pelvic pain, urethral syndrome, urethral stenosis or chronic prostatitis.[1,48,49,56] A common presentation is a patient with irritative voiding complaints refractory to multiple courses of antibacterials, anticholinergics or luteinizing hormone releasing hormone agonists.[48,57-59] Most patients are symptomatic for 2–7 years and see multiple physicians prior to diagnosis with PBS/IC.[1,46-48,60] PBS/IC is generally underdiagnosed, and the delays to diagnosis imply

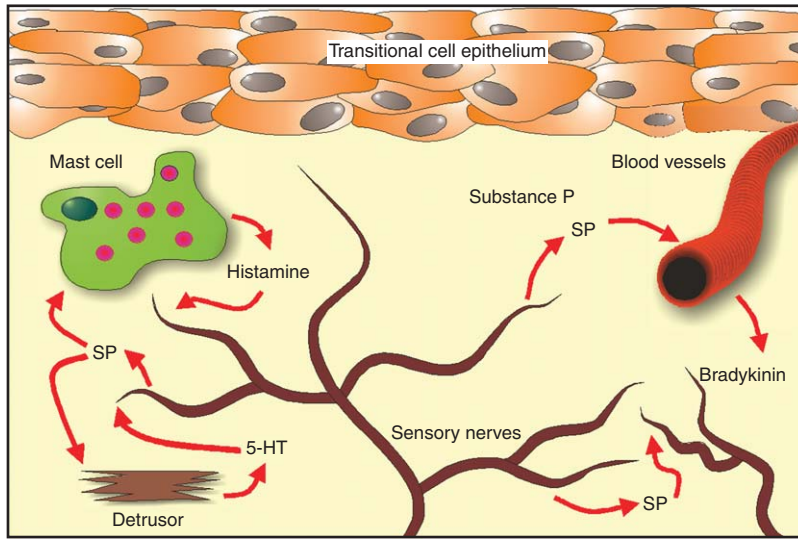

Fig. 1. Neurogenic inflammation in painful bladder syndrome/interstitial cystitis. Activated mast cell in proximity to bladder sensory nerve, with histamine release, leads to substance P (SP) release and sensory nerve transmission. SP also induces further inflammation, including bradykinin and serotonin (5-HT) release, with further nerve activation (reproduced from Dr Robert Moldwin with permission).

Table II. Occurrence of clinical features of painful bladder syndrome/interstitial cystitis in adults and children

Symptom	Adults (%)	Children (%)
Urinary urgency	57–98	88–95
Daytime frequency	84–97	88–100
Pain	66–94	19–81
Nocturia	44–90	21–69
Dysuria	71–98	13
Dyspareunia	46–80	NA
Depression/neurotic symptoms	55–67	13–71

NA = not applicable.

disease progression until the disease severity and full constellation of symptoms makes diagnosis more obvious.[1,5,6,10,40,46-49,56,57] As there is no definite urine test or marker at present, the diagnosis is suspected on the basis of history and physical examination, and other competing disorders are excluded with appropriate testing as warranted.[2,61] A key take-home point is that a high level of suspicion is required because patients may present with a chief complaint of any of urinary frequency, urgency, nocturia, reported 'recurrent bladder infections', pain, dyspareunia or 'painful menses' without these symptoms being linked as relevant.

1.4 Evaluation and Diagnosis

Clinicians should elicit voiding symptoms, daytime frequency and nocturia, history of documented urinary infections and (lack of) response to antibacterials, haematuria, stones and incontinence.[1,48] Many patients will have been misdiagnosed and treated with prior antibacterials, so that many patients will present with reported 'bladder infections that do not respond to normal antibacterials'.[48] The majority of PBS/IC patients are not incontinent.[1,40,48,56] Since OAB and PBS/IC share symptoms of urgency and frequency, some clinicians may mistake PBS/IC for OAB and treat unsuccessfully with antimuscarinic agents.[57] In particular, as early-phase PBS/IC often involves little or no pain, presentation may be strikingly similar. The subjective sense of urgency that is common to PBS/IC and OAB has a subtle but important difference: in PBS/IC, 'urgency' is perceived by patients as a 'compelling urge to urinate that is difficult to postpone', whereas in OAB, 'urgency' is perceived as a 'desire to void with little or no warning'.[62,63] In many PBS/IC patients, urinary urgency is an uncomfortable or painful sensation; when they forestall micturition, urinary urgency and pelvic discomfort or pain increases, which may be a useful clue to suspect PBS/IC, as opposed to OAB where discomfort or pain is unusual.

Pain, pain triggers, mid-cycle or perimenstrual flares, dyspareunia, and localization of dyspareunia to bladder (or anterior vaginal wall) are commonly identified in the medical history of a patient.[1,47,48,54,55,59] Because of symptom progression over time, some patients may present primarily with pelvic pain or dyspareunia, and dismiss their prior, longstanding voiding frequency as normal and unrelated.[1,48,60] Males often report post-ejaculatory pelvic pain, and may present with chronic bacterial prostatitis or chronic nonbacterial prostatitis (chronic pelvic pain syndrome categories 2 and 3, respectively) having been non-responsive to antibacterials, α-adrenergic receptor antagonists or 5-α-reductase inhibitors.[1,48,54,58,64] Food triggers are reported by approximately half of patients.[59] Risk factors for bladder cancer, such as haematuria, cigarette smoking, occupational exposure to carcinogens, pelvic radiation and cyclophosphamide exposure should be identified.[65] Concerns of bladder cancer should be moot in children.

Physical examination typically shows a normal or dysphoric mood, normal abdomen or suprapubic or lower quadrant tenderness, and bladder neck tenderness with or without tenderness in other areas on vaginal examination.[40,66] Rectal examination is typically unremarkable, but rectal tenderness is occasionally present, and may possibly represent evidence of central sensitization.[40,67] Urinalysis and urine culture should be done routinely, and are typically normal. A mid-stream clean-catch urine collection may be difficult to perform, with voided volumes typically <100 mL, and a catheterized specimen may be required to avoid contamination.[1,40,56] Haematuria warrants upper tract imaging and cystoscopy. Urine cytology is warranted in most adults

to exclude bladder carcinoma *in situ*. Many clinicians routinely perform cystoscopy, to exclude other conditions (bladder cancer, bladder stones), although the yield is low.[56,59,65,66]

The traditional diagnostic test of cystoscopy with hydrodistension under anaesthesia is often performed to look for reduced anaesthetic capacity and glomerulations (submucosal petechial haemorrhages after hydrodistension) or Hunner's ulcers.[3] Strict application of these diagnostic criteria is believed to miss the diagnosis in at least 60% of patients.[4] The application of cystoscopy with hydrodistension as a diagnostic test has been challenged, based on low sensitivity and specificity.[68,69] Office cystoscopy using topical anaesthesia is often performed to exclude significant bladder or urethral pathology (bladder tumour, bladder stones, foreign body, urethral stricture).[2] Voiding and fluid intake diaries are helpful, as they demonstrate typically reduced or normal fluid intake, and frequent small voided volumes with little or no incontinence.[1,2,40,48,54,59] Whereas healthy adults typically void approximately 250 mL per void at intervals of approximately 3–4 hours, most PBS/IC patients void ≤100 mL per void at intervals of approximately 1 hour.[1,40,56]

Other diagnostic tests have been described. The potassium test is controversial and is all but impractical for children.[23,49,70] Proponents of the test note that a normal, impermeable urothelium will exclude potassium from crossing the urothelium and so no stimulation of submucosal sensory nerves would occur. In one study, all 47 controls tested negative.[60] PBS/IC patients with abnormal epithelial permeability should test positive.[59] The test is controversial for two reasons. A positive test confirms epithelial dysfunction, whereas a negative test does not exclude disease. Similarly, other proposed diagnostic tests (cystoscopy with hydrodistension, urodynamics, urine biomarkers) have the same limitation: a positive test seems to confirm PBS/IC, whereas a negative test does not necessarily exclude disease.[71] A second source of controversy is that the test can induce bladder pain, and in some instances dramatic bladder pain occurs within seconds of potassium chloride instillation. To our thinking, it validates the utility of the test to reproduce bladder pain. However, it is obvious that urethral catheterization and potassium instillation to reproduce bladder pain is impractical (and in some cases cruel) in younger paediatric patients.

As diagnosis is largely based on history and physical examination, validated questionnaires have been tested to follow or screen patients. The O'Leary Sant index[72] has been validated to follow patients, the pelvic pain urgency frequency (PUF) instrument[73] has been validated to screen patients, and an elevated PUF score has been correlated with a positive potassium test, which allows the clinician to assume a potassium test would probably be positive in a patient with an elevated PUF score.[60] PUF is also more sensitive than the O'Leary Sant index for screening.[74] One difference between the questions in the PUF and O'Leary Sant instruments is that PUF includes questions about pain with intercourse, which may limit its applicability in populations of non-sexually active patients, such as children.

Bladder biopsy is nonspecific and does not diagnose PBS/IC.[1,2,69,75] One promising urine biomarker is APF.[76] APF is specific, but has been tested in NIDDK-criteria patients and may not identify early-phase patients. APF has only been reproduced at one centre[76] and has not been reproduced elsewhere.

Thus, in adult PBS/IC, the syndrome involves the bladder epithelium in the majority of patients, with evidence of abnormal epithelial permeability, mast cell activation in the bladder and, over time, a progressive recruitment of increased sensory afferents in the bladder and pelvis, and a change from mechanoreceptors to pain afferents. Progressively, patients show bladder hypersensitivity and allodynia. Thus, the diagnosis is largely suspected based on irritative voiding symptoms, food triggers, perimenstrual flares, dyspareunia or ejaculatory pain, pelvic pain/pressure/discomfort, a physical examination that is typically normal other than perhaps showing a dysphoric mood, tender abdomen over the suprapubic area and tender bladder neck on vaginal examination, negative urinalysis and urine culture, and lack of response to antibacterials and anticholinergics.[12,46-48,59] Diagnostic tests can

exclude other conditions and may in some patients confirm PBS/IC, but a negative test does not necessarily exclude the diagnosis.[2,71]

1.5 Treatment

Treatment (table III) includes reduction of dietary triggers and stress reduction techniques.[78-80] Calcium glycerophosphate is a compound available in health food stores that, in open-label trials, showed improvement among subjects with food triggers.[81] Based on the finding that urine nitric oxide levels are lower in PBS/IC patients than controls and that L-arginine is a substrate for nitric oxide synthase, L-arginine was tested against placebo in a randomized, double-blind, 3-month trial. Although subjects randomized to L-arginine 1500 mg/day who completed the study fared better than controls, on an intent-to-treat analysis there was no difference between cohorts.[82]

Oral pentosan polysulfate proved efficacious in randomized double-blind trials when compared with placebo.[83-85] In these three trials, patients randomized to pentosan showed 3-month success rates (different endpoints in each trial) of 28–44%, whereas patients randomized to placebo showed 3-month success rates of 13–16%, with statistically significant differences between treatment and placebo groups in all three trials. Another trial showed negative results for global response, but reductions in pain and increases in bladder capacity in pentosan-treated subjects versus placebo recipients.[86] One underpowered 2×2 randomized trial comparing oral pentosan, hydroxyzine, pentosan combined with hydroxyzine, and placebo showed a trend

Table III. Treatment approaches for painful bladder syndrome/interstitial cystitis

Treatment	Mechanism of action	Suggested approach/dose	Paediatric dose	Adverse effects
Dietary management	Reduce triggers	http://www.ichelp.org[77]	http://www.ichelp.org[77]	Lack of citrus in diet
	Neutralize triggers	Calcium glycerophosphate 2 tablets before food trigger	Calcium glycerophosphate 1–2 tablets before food trigger	Unknown
Lifestyle modification	Possible stress reduction	Yoga, relaxation techniques	Yoga, relaxation techniques	Unknown
Pelvic floor physiotherapy	Possible myofascial release	Pelvic floor myofascial release	Pelvic floor myofascial release	Not tested or reported in children
Pentosan polysulfate	Presumed epithelial mucin coating	100 mg PO tid	100 mg PO bid to tid	GI, alopecia
Hydroxyzine	Stabilize mast cells	25–50 mg PO qhs	10–25 mg PO qhs	Sedation
Cimetidine	H_2 receptor antagonist	400 mg PO bid	≤12 years: 20–25 mg/kg/day divided q6 administration; age >12 y: adult dose	Neurotoxicity
Amitriptyline	Pain reduction	25–75 mg PO qhs	Adolescents: 10–25 mg PO qhs	Sedation, dry mouth, arrythmia, constipation, weight gain
Gabapentin	Neuromodulation	300–900 mg PO qhs	10–15 mg/kg qhs, may increase in 10 mg/kg increments, maximum 50 mg/kg	Sedation, nightmares
Intravesical dimethyl sulfoxide	Multiple mechanisms	50% solution 50 mL every week	50% solution 50 mL every week	Garlic breath, bladder pain with instillation
Intravesical 'therapeutic solution'	Downregulate sensory nerves, coat epithelium	2% lidocaine 8 mL, 8.4% HCO_3 4 mL, heparin 2 mL (10 000 U/mL) 3 times per week for 3 weeks	35 kg: half adult dose ≥45 kg: adult dose	Lidocaine toxicity if overdosed, bladder infection

bid = twice daily; **DMSO** = dimethyl sulphoxide; **GI** = gastrointestinal; **H** = histamine; **HCO_3** = bicarbonate; **PO** = orally; **q6** = every 6 h; **qhs** = daily 1-2 h before sleep; **tid** = three times daily.

towards better response with pentosan than placebo ($p = 0.06$).[87] A meta-analysis assessing the efficacy of pentosan concluded that it is efficacious compared with placebo.[88]

Pentosan is believed to coat the bladder epithelium and restore the permeability barrier. Other mechanisms have been shown and the precise mechanism by which PBS/IC patients improve on pentosan is not known.[89] The drug is poorly absorbed across the gastrointestinal tract and only its low-molecular-weight portion, comprising 6%, is excreted in urine.[90,91]

In an early compassionate-use open-label trial, patients whose previous treatments had failed were offered the opportunity to take pentosan at their cost and were followed-up for up to 116 months.[92] At study end, only 11% of patients were still taking the drug, with only 6% taking it continuously for ≥18 months. This study has been cited as evidence that on an intent-to-treat basis, the response rate is low and most patients discontinue treatment. A contrary view comes from a randomized, blinded, dose-ranging trial in which, even accounting for patient withdrawals, regardless of dose, patient response rates improved sequentially at 1, 3 and 6 months.[93] Some patients will stop medication as a result of lack of efficacy within the first few months and it is worthwhile to explain to patients at the outset that any benefit is likely to become apparent only after they have been taking pentosan continuously for at least 3–6 months. We infer that the bulk of randomized, prospective data show drug efficacy compared with placebo using various outcomes and analyses, but note that a response may require months of continuous therapy.

Hydroxyzine may be clinically useful. In a randomized, double-blind placebo-controlled trial, in which hydroxyzine, pentosan and the combination of both drugs were compared, combination therapy showed the greatest efficacy ($p = 0.07$), although the study was underpowered.[87] The interpretation of the study data was controversial, with the authors concluding that hydroxyzine is ineffective. Others (ourselves included) believe the statistical trend is consistent with good clinical results seen in some patients, particularly patients with atopic histories.[94] A subset of patients have mast cells and histamine in the bladder, suggesting that hydroxyzine should be efficacious.[27,35] Similarly, a randomized, double-blind trial of the histamine H_2-receptor antagonist cimetidine (400 mg orally twice daily) versus placebo for 3 months showed efficacy among subjects randomized to cimetidine, with reductions in symptom score, nocturia and suprapubic pain.[95] Interestingly, all patients had initial bladder biopsies showing a chronic inflammatory infiltrate. There was no apparent difference in mast cell findings on bladder biopsy before and after cimetidine. In *in vitro* experiments, pentosan demonstrates antihistamine activity.[89]

Low-dose amitriptyline is widely used to minimize visceral pain and has been proven effective in randomized double-blind trials.[96] Some recent unblinded trials have shown efficacy using immune modulators such as ciclosporin, albeit with significant adverse effects.[97,98] Off-label use of gabapentin has been used, although no data have been published on its efficacy for PBS/IC.

Intravesical therapy includes repetitive instillations of various medications, such as dimethyl sulfoxide (DMSO), pentosan, the combination of lidocaine with heparin and bicarbonate ('therapeutic solution'), bacillus Calmette-Guérin (BCG), and chondroitin sulfate.[99-102] DMSO was the first therapy approved for IC in the US. DMSO was superior in a prospective, randomized, double-blind study comparing intravesical DMSO versus BCG, showing reductions in pain in both non-ulcer and ulcer forms of IC, and reductions in frequency in ulcer forms of IC.[103] A Cochrane review of intravesical therapies concluded that data on intravesical DMSO were limited, generally showing no apparent differences from placebo.[104] The profound garlic breath patients experience with DMSO will likely prevent truly blinded trials from being conducted.[105] Intravesical botulinum toxin A has been advocated by some, but results have been unsatisfactory.[106] Intravesical 'therapeutic solution' has been tested with various combinations of lidocaine and bicarbonate, with or without heparin.[59,100,101,107] Alkalinized lidocaine crosses the urothelium and it is thought that it

downregulates bladder sensory afferents.[100,108] In a randomized double-blind trial, a combination of lidocaine and bicarbonate was proven to be effective compared with placebo.[107] Open-label trials with combined lidocaine, heparin and bicarbonate show efficacy for voiding frequency, nocturia, pain, dyspareunia and multiple domains of female sexual function.[100,101,109]

In particular, urethral dilations have long been advocated by some clinicians.[110] This procedure is less often used currently than historically.[111] There appears to be no compelling data to support its use, with little evidence that patients have urethral stenosis or that patients benefit.[1,56]

2. PBS/IC in Children

2.1 PBS/IC is Similar in Children and Adults

PBS/IC in children has been subject to few reports and the reports are mostly from older literature. These reports are from previous eras when IC was diagnosed only in the setting of a suggestive history and physical examination, with a cystoscopy with hydrodistension under anaesthesia showing a reduced bladder capacity and submucosal petechial haemorrhages (glomerulations) or a denuded patch of urothelium (Hunner's ulcer).[12-16] Thus, these older publications of paediatric PBS/IC reported only on children with more severe disease (NIDDK-type criteria) compared with the more current (and controversial) practice of diagnosing patients based on clinical criteria, so there may be some selection bias. Notwithstanding these concerns, these older reports show that children with PBS/IC present similarly to adult PBS/IC patients. Children in these reports presented mostly with urinary frequency, and also had evaluations that were negative for infection, tumour, stones or any obvious pathology to explain their symptoms. In one 1970 report from a large paediatric urology practice, 21 cases were identified. The chief complaint was frequency and the second most common complaint was enuresis.[14,112] In a more recent report, of 16 patients, 88% presented with frequency and sensory urgency and 81% had lower abdominal pain relieved by voiding.[16]

A caveat in the paediatric PBS/IC reports is that diagnosis was established by cystoscopy with hydrodistension under anaesthesia showing reduced anaesthetic bladder capacity, submucosal petechial haemorrhages (glomerulations) or Hunner's ulcer. Bladder biopsy findings were nonspecific, as reported in adult series. By relying on NIDDK-type criteria, it is possible that patients with less severe, early-phase disease were missed.[4,56,113] Temporary symptom improvement after anaesthetic cystoscopy with hydrodistension was also reported.[16] In the 1970 publication, one of the diagnostic criteria was 'dramatic relief of symptoms after diagnostic distension', so 100% of paediatric PBS/IC patients responded.[14] Given that adult series of PBS/IC generally note a 60% response rate to anaesthetic hydrodistension, it is possible that the authors defined paediatric PBS/IC arbitrarily, as they excluded children whose therapy failed. In a 2006 publication in which 18 PBS/IC patients aged 15–25 years were studied, 55% of subjects responded to hydrodistension, similar to adult data.[56,113]

Behavioural issues (neurotic behaviour, chronic anxiety, environmental stressors) were also commonly identified in paediatric PBS/IC reports, not dissimilar to adult presentation.[12,14,16] In effect, children with PBS/IC present remarkably similarly to adults with PBS/IC (table I).

A review article from 2004 articulated the dilemma in paediatric PBS/IC.[114] The diagnostic criteria are debatable, the NIDDK criteria exclude the diagnosis under age 18 years, and the literature hints that patients tend to progress over time if left untreated. The concern is that a child presenting with suggestive symptoms should prompt PBS/IC within the differential diagnosis; diagnosis should be expeditious so symptoms can be controlled, and also to prevent progression that may occur if left untreated. As stated by Ratner: "Many urologists think that IC does not exist in the pediatric patient population, or that it is exceedingly rare. Many cases of voiding dysfunction in children are self-limiting. How many of these cases are actually early IC…?… Should we be aggressively treating these children who exhibit signs of voiding dysfunction or IC in early

childhood to avoid the re-emergence of the disease later in life? Or are the risks of general anesthesia and a major urologic workup too great in children whose symptoms may spontaneously resolve, never to re-appear? Would early treatment of children with symptoms of IC increase the chances of permanent remission? Approximately 25% of IC patients report that they were plagued with chronic urinary tract problems as children''.[115] What diagnostic criteria in children would be sufficient for a clinician to feel confident of diagnosis and to initiate long-term therapy?[116] It is likely this question will not be answered satisfactorily until a diagnostic marker is demonstrated and gains acceptance. In the meantime, clinicians who care for paediatric PBS/IC patients will face the same dilemma that urologists with adult patients face.

An obvious challenge in diagnosing paediatric PBS/IC on the basis of clinical presentation is that the presenting symptoms and signs attributable in adult PBS/IC may not translate to children. Dyspareunia is seen in 46–87% of adult patients.[10,53-55] (One hopes that) children are not sexually active. Dyspareunia may be present in some adolescents. Similarly, perimenstrual and menstrual flares cannot occur in the premenarchal age group. Up to one-third of adults with PBS/IC have a history of prior sexual abuse or domestic violence that may have produced longstanding central sensitization.[40,44] It may be difficult to elicit such information in the typical setting where the child is accompanied by their parent. The physical examination in adults is useful to exclude any obvious mimicking disorders (vulvodynia, vaginitis, vaginal or cervical infection, active genital herpes, pelvic floor dysfunction, cervical motion tenderness, rectal tenderness or faecal impaction).[1,3,40,41] Many children and adolescents will not or cannot participate in a vaginal and rectal examination to detect tender areas. The remaining aspects of history and examination that can typically be elicited then are as follows: voiding frequency, nocturia, continence, urinary infection, food and fluid intake history and triggers, pain, and abdominal and back examination. Thus, the paediatrician is limited in their ability to discriminate PBS/IC from multiple other mimicking disorders using clinical criteria.

2.2 Evaluation and Diagnosis

History and physical examination should elicit voiding frequency, nocturia, age of toilet training, continence, enuresis, bowel habits, urinary infections and haematuria. A voiding and fluid intake diary may be instructive. Healthy children typically void 5–6 times per day, with a slight decrease in the number of daily voids as children age.[117] In adults, PBS/IC patients typically void approximately every hour or more frequently. Thus, it seems logical that, as healthy children void as frequently as healthy adults, a child with increased voiding frequency (>8 times per day) is unusual, and certainly a voiding frequency bordering on every hour is statistically abnormal.[118,119] Young children may localize pain poorly (abdomen, pelvis, suprapubic area, urethra, vagina, perineum), and often describe pain or dysuria after drinking citrus or cranberry juice or cola beverages.[16,115] Dietary triggers, pain triggers, menstrual history and social stressors should also be elicited. Voiding frequency is the most common chief complaint among paediatric PBS/IC patients.[12-16,114] Posturing, squatting, Vincent's curtsy or any signs of motor urgency are invariably absent.[16] In the senior author's (Teichman) experience, several observations of paediatric PBS/IC seem consistent: paediatric PBS/IC typically presents as voiding frequency and pelvic pain or discomfort, often associated with specific food triggers. Paediatric PBS/IC patients often do not present with nocturia, perimenstrual flares or dyspareunia, except in older adolescents.[16] Moreover, many paediatric PBS/IC patients have had urodynamic testing prior to referral, and all have had low volumes of first sense of filling, first urge to void and capacity, with normal compliance, no unstable detrusor contractions and normal voiding parameters. In other words, urodynamics consistently show hypersensitivity.

However, there are other conditions associated with increased voiding frequency, including bacterial cystitis, bladder stone or foreign

body, vesicoureteral reflux (with 'yo-yo' of urine between bladder and upper tracts), neurogenic bladder, extraordinary urinary frequency of childhood and dysfunctional voiding. Bladder-associated pain would suggest PBS/IC, bacterial cystitis, bladder stone or foreign body. However, the absence of pain may not necessarily exclude PBS/IC. A urinalysis and urine culture should identify infection or haematuria, which should prompt consideration of several of these conditions and appropriate testing. Neurogenic bladder should be suspected on the basis of history and examination (back and spine, gait, perineal sensation). In the presence of documented urinary infection or haematuria, a renal and bladder ultrasound is indicated, although it is common practice for many paediatricians and urologists to order an ultrasound for any of the presentations discussed previously. A voiding and fluid intake diary may be beneficial in the evaluation of any child with frequency, whether they have PBS/IC or not. The diary is non-invasive and provides documentation of voided volumes, voiding frequency, nocturia, incontinence and also fluid intake. The occasional patient will have a large fluid intake or large intake of caffeinated drinks, which might not be recognized simply by history.[1,2,48,56] According to published reports on PBS/IC in children, examination is almost always unremarkable except for frequent observation of 'anxiety'.[14,16] Pelvic examination may reproduce pain on bladder base palpation, but it is likely that most children will not permit an adequate pelvic examination.[114]

A separate condition of extraordinary urinary frequency in childhood has been reported.[120-123] This condition is described as abnormally increased diurnal frequency in a completely toilet-trained child with normal urinalysis. Of the four studies listed, some important points emerge. There was roughly equivalent distribution between boys and girls, ages were 2–14 years, onset was typically sudden, and almost all children had normal kidneys and kidney function, lack of urinary or systemic infection, and normal tests. Spontaneous resolution after several months was commonly observed, although long-term follow-up was not specified. Common themes were psychosocial stressors (14 of 26 children in one study[123] and 22 of 28 children in another study[120]) and occurrence of symptoms during the school year.[115,121,122] Antibacterials and anticholinergic agents were ineffective.[121,123] In one study,[123] 9 of 26 children had large intakes of provocative beverages (black or ice tea; orange, apple, grape, grapefruit or tomato juices; acidic juices). Once these beverages were eliminated, symptoms resolved in 7 of 9 children. In other words, it is unclear whether extraordinary urinary frequency of childhood is a separate disease entity or PBS/IC. A dilemma is that daytime frequency in the absence of any other symptoms may be isolated and self-limited, and not require any further work-up or therapy.[116] A reasonable approach would be to exclude infection, eliminate food triggers and re-evaluate.

Dysfunctional voiding is a nonspecific term in the paediatric urology literature, and does not connote one specific underlying disorder. It is estimated that dysfunctional voiding accounts for 20–30% of the typical paediatric urology practice. It includes children with urinary tract infection, constipation or encopresis, inappropriate sphincter relaxation (failure of sphincter relaxation during micturition) and the 'urge syndrome' (idiopathic detrusor instability in children). In these varying conditions, when treated with conservative measures (biofeedback, anticholinergics, psychological counselling), 87–91% of children show resolution with long-term follow-up (over 2.5 years).[124,125] Approximately 10% of children with urge syndrome do not respond to these conservative measures.[124,125] Thus, a child with urgency/frequency who does not respond to these therapies should prompt consideration of either further diagnostic testing (urodynamics) or an alternative diagnosis (such as PBS/IC).

There are no accepted confirmatory tests for diagnosis, even in adult PBS/IC.[2] A consistent dilemma has been that a positive test indicates disease, whereas a negative test does not necessarily exclude disease.[71] The literature on PBS/IC demonstrates that paediatric urologists traditionally have diagnosed PBS/IC only in the presence of cystoscopic and hydrodistension

findings of submucosal petechial haemorrhages (glomerulations) or Hunner's ulcer.[12-16] However, similar to adults, children thought clinically to have PBS/IC may not show positive findings (glomerulations, Hunner's ulcer or reduced anaesthetic capacity).[126] It is relevant for clinicians to understand that positive findings (glomerulations, Hunner's ulcers, aged-adjusted reduced capacity) may be instructive, but negative findings do not exclude disease, and clinicians will still face the dilemma of treating in the presence of negative findings.[56,68,69,71,114] Some authors advocate urodynamic tests in children to exclude detrusor instability and to confirm sensory urgency (small capacity bladder with early sensation and urgency).[16] We and others advocate that a voiding diary is likely to provide as much information.[59,114,126] A recently proposed test is to place 'therapeutic solution' (a combination of lidocaine, heparin and bicarbonate; see table III) into the bladder for 1 hour. If pain is reduced by >50%, the test is considered positive.[59,71,107,108] Few data are available on the use of 'therapeutic solution' as a diagnostic test, but it is better tolerated than a potassium test, probably has similar caveats (a negative test may mean little) and would only be useful if the child had pelvic pain at the visit at which the test was performed. In the end, the clinician will diagnose children with PBS/IC primarily on the basis of clinical presentation, negative urinalysis and urine culture, with or without confirmatory findings on any of the proposed tests (table IV).

Historically, many of these symptomatic children (and adults) would have been treated for urethral stenosis. This diagnosis is controversial. True urethral stenosis is rare. Even in 16 adult patients who presented to our care with this diagnosis, all easily accommodated passage of a 22 Fr cystoscope in the urethra.[56] We think urethral stenosis is a misdiagnosis in most patients and probably represents PBS/IC. This point is not trivial, as our experience indicates that many young women (aged around 20 years) who we diagnose with PBS/IC often describe other care providers as having performed urethral dilations at onset of symptoms, typically 3–5 years earlier.[110,111] However, older data obtained on asymptomatic girls showed that the mean diameter of the urethra ranges from 14 Fr in 2-year-olds to 27 Fr in 18-year-olds.[112] Even in newborn girls, the mean calibre is 16 Fr.[127] Barring documentation of urethral calibre <14 Fr, urethral stenosis is not an appropriate consideration, and urethral dilation, although sometimes performed in children with dysfunctional voiding, has no scientific basis.[128]

2.3 Treatment

There are no available randomized, blinded therapeutic trials of paediatric PBS/IC, so the only published data represent retrospective series, with no peer-reviewed published data more recent than 1996. Treatment of paediatric PBS/IC includes dietary and fluid management. Most

Table IV. Evaluation of suspected paediatric painful bladder syndrome/interstitial cystitis (PBS/IC)

Evaluation/diagnostic test	Mandatory/optional	Useful data consistent with PBS/IC
History	Mandatory	Urgency, frequency, nocturia, pain
Physical	Mandatory	Normal, or suprapubic or bladder tenderness
Urinalysis and culture	Mandatory	Negative
Voiding diary	Optional (recommended)	Normal or reduced fluid intake, frequent small voided volumes
Validated instruments (pain urgency frequency, O'Leary Sant)	Optional	Increased scores
Urodynamics	Optional	Sensory urgency
Alkalinized lidocaine challenge	Optional	Reduction in pain with instillation
Renal/bladder ultrasound	Optional	Indicated for other urologic considerations
Cystoscopy with hydrodistension under anaesthesia	Optional	Hunner's ulcer, reduced anaesthetic capacity, glomerulations

paediatric patients or their parents (and clinicians) are unwilling to initiate amitriptyline for a paediatric condition. In the older adolescent, amitriptyline 10–75 mg 1 hour before bedtime may be indicated to reduce neural activation and upregulation (i.e. reduce pain). It is important to educate the patient that amitriptyline is being used off-label for pain control, otherwise some patients upon reading the pharmacy printout of this antidepressant may falsely assume that you are dismissing their complaints and treating them as 'crazy'.[59] In a randomized double-blind study of adult PBS/IC patients in which patients could self-titrate the drug, the mean dose was 55 mg.[96] Adverse effects included fatigue, dry mouth, constipation, palpitations, weight gain and urinary retention, and were dose dependent. Gabapentin is often used in adults at high doses (up to 900 mg orally three times daily) off-label for pain control, particularly when amitriptyline is ineffective or not tolerated. Given its adverse effects of sedation and nightmares, we think many clinicians would be reluctant to use gabapentin in children.[59]

Pentosan polysulfate is indicated only in adults and no safety studies have been conducted in patients aged <18 years. The approved dosage is 100 mg three times daily for an adult (70 kg). Dose administration is by bodyweight, for example a 40-kg child would be administered 100 mg twice daily. The main adverse effects are digestive signs (gastrointestinal discomfort, diarrhoea) and alopecia (usually more strands of hair fall out with combing or brushing, rather than chemotherapy-type baldness), each occurring in <4% of patients. Long-term therapy (>3 months) is typically required in adults and continuous administration is required for persistent efficacy.[93] Without safety studies in children, we cite animal data showing pentosan administered to rats aged up to 2 years in doses of up to 252 mg/kg five times per week had no carcinogenic activity in most strains of rats; however, in one strain of rats, increased liver haemangiosarcomas were seen at a dose of 504 mg/kg but not at lower doses.[129] Inflammatory findings in bowel, liver or lymph nodes were seen at doses >250 mg/kg in 3-month studies. These animal data provide reasonable assurance of the safety of long-term pentosan at typical doses (<5 mg/kg/day). However, without published data on pentosan efficacy and safety in children, some clinicians may feel reluctant to initiate long-term therapy, even with proven efficacy and safety in adults.

Hydroxyzine is a combined-action anxiolytic-antihistamine. Its main adverse effect is sedation, which usually improves once tolerance occurs, typically after 3–4 weeks of continuous administration.[59,94] The adult dose is typically 10–50 mg, and the usual dose is 25 mg taken 1 hour before bedtime.[87] In children aged <12 years, hydroxyzine may be administered at 5–10 mg at bedtime. The adult PBS/IC literature supports use of the H_2-receptor antagonist cimetidine.[95] There are no published studies for paediatric PBS/IC using cimetidine. Its use for gastroesophageal reflux disease shows it can be safely used in children.[130] Cimetidine may be a reasonable alternative to hydroxyzine without risk of sedation. A dosage regimen is shown in table III.

Intravesical instillations of therapeutic solution have not been reported in children, although our anecdotal experience with adolescents suggests it is well tolerated and works as well as it does in adults. After 'coaching' adolescent patients to try a single instillation, we have seen these patients return weeks later asking for repeat instillations. Intravesical DMSO has been reported to work initially in a case report of a 4-year-old girl, although the authors commented that she required additional intravesical therapy with an unspecified second-line regimen.[131] DMSO sometimes produces transient pain, in addition to a profound garlic breath. We believe many clinicians would prefer therapeutic solution over DMSO as instillation therapy for paediatric PBS/IC patients. Although opioid analgesics are sometimes used in adult patients with refractory pain, it is likely that many clinicians would be reluctant to place children on long-term opioids.

An issue that has emerged with adult experience in managing PBS/IC is that management is long term.[71] Using the experience with oral pentosan as a benchmark (since it is as well studied as any other treatment for PBS/IC),

one factor contributing to success of treatment is long-term compliance.[93] Similarly, the adult responder rate increases over time, so that, although approximately 20–25% of adult patients respond at 1 month, over 50% of patients are responders by 6 months.[93] It is likely that once neural activation and upregulation have occurred, downregulation does not necessarily occur as soon as the bladder is treated.[71] Central sensitization may also be an important factor.[33,38,39] Downregulation may take months after treatment of the bladder is implemented. For these reasons, when a diagnosis is made and management instituted, it is worthwhile to set realistic expectations with the patient (and parents) that initial response may take months, management may be long term, and dietary and lifestyle compliance may be important. In particular, for the prepubescent PBS/IC patient, symptoms may flare at the onset of menarche (and may require the addition of antihistamines) and may be triggered if the adolescent becomes sexually active. Our own experience, although limited with this population, is similar to that in other chronic diseases of childhood in that some adolescents 'rebel' and become less compliant with their therapy. The clinician must be patient and persistent to try to re-educate these patients about their disease and management.

3. Conclusions

PBS/IC presents similarly in both adults and children. The most common paediatric presentation of PBS/IC is urinary frequency and abdominal pain is also common. Food triggers are described in a subset of adults and children. Unlike adults, enuresis may be a common presenting feature in children. Common adult triggers such as menses and vaginal intercourse may not be relevant in children. Diagnosis is by exclusion and there is currently no definitive test. Management includes dietary and lifestyle modifications. Lack of data on outcomes of paediatric PBS/IC treated with pharmacological agents makes firm recommendations problematic, although pentosan, amitriptyline, hydroxyzine and cimetidine may be options. Intravesical options include 'therapeutic solution' or DMSO. It is important that patients are treated long term.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Teichman serves as a consultant for Ortho-McNeil and owns stock in Urigen Pharmaceuticals.

References

1. Teichman JMH, Parsons CL. Contemporary clinical presentation of interstitial cystitis. Urology 2007; 69 Suppl. 4A: 41-7
2. Nickel JC. Interstitial cystitis: the paradigm shifts – international consultations on interstitial cystitis. Rev Urol 2004; 6: 200-2
3. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases Workshop on Interstitial Cystitis. J Urol 1988; 140: 203-6
4. Hanno PM, Landis JR, Matthews-Cook Y, et al. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. J Urol 1999; 161: 553-7
5. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol 2005; 174: 2231-4
6. Clemens JQ, Meenan RT, Rosetti MC, et al. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005; 173: 98-102
7. Curhan GC, Speizer FE, Hunter DJ, et al. Epidemiology of interstitial cystitis: a population based study. J Urol 1999; 161: 549-52
8. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. Urology 1997; 49 Suppl. 5A: 2-9
9. Leppilahti M, Sairanen J, Tammela TL, et al. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. J Urol 2005; 174: 581-3
10. Parsons CL, Tatsis V. Prevalence of interstitial cystitis in young women. Urology 2004; 64: 866-70
11. Parsons JK, Kurth K, Sant GR. Epidemiologic issues in interstitial cystitis. Urology 2007; 69 Suppl. 4A: 5-8
12. McDonald HP, Upchurch WE, Sturdevant CE. Interstitial cystitis in children. J Urol 1953; 79: 890-3
13. Chenoweth CV, Clawater Jr EW. Interstitial cystitis in children. J Urol 1960; 83: 150-2
14. Geist RW, Antolak SJ. Interstitial cystitis in children. J Urol 1970; 204: 922-25
15. Farkas A, Waisman J, Goodwin WE. Interstitial cystitis in adolescent girls. J Urol 1977; 118: 837-9
16. Close CE, Carr MC, Burns MW, et al. Interstitial cystitis in children. J Urol 1996; 156: 860-2
17. Held PJ, Hanno PM, Wein AJ, et al. Epidemiology of interstitial cystitis. In: Hanno PM, Staskin DR, Krane RJ,

et al., editors. Interstitial cystitis. New York: Springer-Verlag, 1990: 29-48

18. Pauwels E, De Wachter S, Wyndaele JJ. Normality of bladder filling studied in symptom-free middle-aged women. J Urol 2004; 171: 1567-70
19. Su X, Sengupta JN, Gebhart GF. Effects of opioids on mechanosensitive pelvic nerve afferent fibers innervating the urinary bladder of the rat. J Neurophysiol 1977; 77: 1566-80
20. Parsons CL, Stauffer C, Schmidt JD. Bladder-surface glycosaminoglycans: an efficient mechanism of environmental adaptation. Science 1980; 208: 605-7
21. Parsons CL, Boychuk D, Jones S, et al. Bladder surface glycosaminoglycans: an epithelial permeability barrier. J Urol 1990; 143: 139-42
22. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol 1991; 145: 732-5
23. Parsons CL, Greenberger M, Gabal L, et al. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998; 159: 1862-7
24. Slobodov G, Feloney M, Gran C, et al. Abnormal expression of molecular markers for bladder impermeability and differentiation in the urothelium of patients with interstitial cystitis. J Urol 2004; 171: 1554-8
25. Hurst RE, Moldwin RM, Mulholland SG. Bladder defense molecules, urothelial differentiation, urinary biomarkers, and interstitial cystitis. Urology 2007; 69 Suppl. 4A: 17-23
26. Saban MR, Nguyen NB, Hammond TG, et al. Gene expression profiling of mouse bladder inflammatory responses to LPS, substance P, and antigen-stimulation. Am J Pathol 2002; 160: 2095-10
27. Sant GR, Kempuraj D, Marchand JE, et al. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. Urology 2007; 69 Suppl. 4A: 34-40
28. Kastrup J, Hald T, Larsen S, et al. Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. Br J Urol 1983; 55: 495-500
29. Letourneau R, Sant GR, El-Mansoury M, et al. Activation of bladder mast cells in interstitial cystitis. Int J Tissue React 1992; 14: 307-12
30. Christmas TJ, Rode J, Chapple CR, et al. Nerve fibre proliferation in interstitial cystitis. Virchows Arch A Pathol Anat Histopathol 1990; 416: 447-51
31. Steers WD, Tuttle JB. Neurogenic inflammation and nerve growth factor: possible roles in interstitial cystitis. In: Sant GR, editor. Interstitial cystitis. Philadelphia (PA): Lippincott-Raven, 1997: 67-75
32. Lowe EM, Anand P, Terenghi G, et al. Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis. Br J Urol 1997; 79: 572-7
33. Nazif O, Teichman JMH, Gebhart GF. Neural upregulation in interstitial cystitis. Urology 2007; 69 Suppl. 4A: 24-33
34. Teichman JMH, Moldwin R. The role of the bladder surface in interstitial cystitis/painful bladder syndrome. Can J Urol 2007; 14: 3599-607
35. Theoharides TC, Kempuraj D, Sant GR. Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. Urology 2001; 57 Suppl. 6A: 47-55
36. Hofmeister MA, He F, Ratliff TL, et al. Mast cells and nerve fibers in interstitial cystitis (IC): an algorithm for histologic diagnosis via quantitative image analysis and morphometry (QIAM). Urology 1997; 49 Suppl. 5A: 41-7
37. Wesselmann U. Neurogenic inflammation and chronic pelvic pain. World J Urol 2001; 19: 180-5
38. Lutgendorf SK, Latini JM, Rothrock N, et al. Autonomic response to stress in interstitial cystitis. J Urol 2004; 172: 227-31
39. Lutgendorf SK, Kreder KJ, Rothrock NE, et al. Diurnal cortisol variations and symptoms in patients with interstitial cystitis. J Urol 2002; 167: 1338-43
40. Seth A, Teichman JMH. Differences in the clinical presentation of interstitial cystitis/painful bladder syndrome patients with and without history of sexual abuse. J Urol 2008; 180: 2029-33
41. Erickson DR, Morgan KC, Ordille S, et al. Nonbladder related symptoms in patients with interstitial cystitis. J Urol 2001; 166: 557-62
42. Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 1994; 107: 271-93
43. Lutgendorf SK, Kreder KJ, Rothrock NE, et al. Stress and symptomatology in patients with interstitial cystitis: a laboratory stress model. J Urol 2000; 164: 1265-9
44. Peters KM, Kalinowski SE, Carrico DJ, et al. Fact or fiction: is abuse prevalent in patients with interstitial cystitis? Results from a community survey and clinic population. J Urol 2007; 178: 891-5
45. Warren JW, Keay SK, Meyers D, et al. Concordance of interstitial cystitis in monozygotic and dizygotic twin pairs. Urology 2001; 57 Suppl. 6A: 22-5
46. Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). J Urol 1949; 61: 291-310
47. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978; 12: 381-92
48. Driscoll AM, Teichman JMH. How do patients with interstitial cystitis present? J Urol 2001; 166: 2118-20
49. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology 2001; 57: 428-32
50. Bjorling DE, Wang ZY. Estrogen and neuroinflammation. Urology 2001; 57 (6 Suppl. 1): 40-6
51. Powell-Boone T, Ness TJ, Cannon R, et al. Menstrual cycle affects bladder pain sensation in subjects with interstitial cystitis. J Urol 2005; 174: 1832-6
52. Shorter B, Lesser M, Moldwin RM, et al. Effect of comestibles on symptoms of interstitial cystitis. J Urol 2007; 178: 145-52
53. Warren JW, Brown J, Tracy JK, et al. Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. Urology 2008; 71: 444-8
54. Ottem DP, Carr LK, Perks AE, et al. Interstitial cystitis and female sexual dysfunction. Urology 2007; 69: 608-10
55. Peters KM, Killinger KA, Carrico DJ, et al. Sexual function and sexual distress in women with interstitial cystitis: a case-control study. Urology 2007; 70: 543-7

56. Ottem DP, Teichman JMH. What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005; 66: 494-9
57. Minaglia S, Ozel B, Bizhang R, et al. Increased prevalence of interstitial cystitis in women with detrusor overactivity refractory to anticholinergic therapy. Urology 2005; 66: 702-6
58. Nickel JC, Teichman JMH, Gregoire M, et al. Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE study. Urology 2005; 66: 935-40
59. Teichman JMH. Painful bladder syndrome: a chronic condition. Can J Diagnosis 2008; 25: 97-101
60. Parsons CL, Dell J, Stanford EJ, et al. The prevalence of interstitial cystitis in gynecologic patients with pelvic pain, as detected by intravesical potassium sensitivity. Am J Obstet Gynecol 2002; 187: 1395-400
61. Payne CK, Terai A, Komatsu K. Research criteria versus clinical criteria for interstitial cystitis. Int J Urol 2003; 10 Suppl.: S7-10
62. Diggs C, Meyer WA, Langenberg P, et al. Assessing urgency in interstitial cystitis/painful bladder syndrome. Urology 2007; 69: 210-4
63. Greenberg P, Brown J, Yates T, et al. Voiding urges perceived by patients with interstitial cystitis/painful bladder syndrome. Neurourol Urodyn 2008; 27: 287-90
64. Parsons CL, Albo M. Intravesical potassium sensitivity in patients with prostatitis. J Urol 2002; 168: 1054-7
65. Tissot WD, Diokno AC, Peters KM. A referral center's experience with transitional cell carcinoma misdiagnosed as interstitial cystitis. J Urol 2004; 172: 478-80
66. Peters KM, Carrico DJ. Frequency, urgency, and pelvic pain: treating the pelvic floor versus the epithelium. Curr Urol Rep 2006; 7: 450-5
67. Warren JW, Langenberg P, Greenberg P, et al. Sites of pain in interstitial cystitis/painful bladder syndrome. J Urol 2008; 180:1373-7
68. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. J Urol 1998; 160: 1663-1667
69. Denson MA, Griebling TL, Cohen MB, et al. Comparison of cystoscopic and histologic findings in patients with suspected interstitial cystitis. J Urol 2001; 164: 1908-11
70. Teichman JM, Nielsen-Omeis BJ. Potassium leak test predicts outcome in interstitial cystitis. J Urol 1999; 161: 1791-6
71. Seth A, Teichman JMH. What's new in painful bladder syndrome/interstitial cystitis? Curr Opin Urol 2008; 9: 349-57
72. Leary MP, Sant GP, Fowler Jr FJ, et al. The interstitial cystitis symptom index and problem index. Urology 1997; 49 (Suppl. 5A): 58-63
73. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. Urology 2002; 60: 573-8
74. Kushner L, Moldwin RM. Efficiency of questionnaires used to screen for interstitial cystitis. J Urol 2006; 176: 587-92
75. Evans RJ, Sant GR. Current diagnosis of interstitial cystitis: an evolving paradigm. Urology 2007; 69 Suppl. 4A: 64-72
76. Keay SK, Zhang CO, Shoenfelt J, et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. Urology 2001 Jun; 57 (6 Suppl. 1): 9-14
77. Interstitial Cystitis Association. Diet [online]. Available from URL: http://www.ichelp.org/Treatments/Self-help/Diet/tabid/247/Default.aspx [Accessed 2009 Feb 17]
78. Spanos C, Pang X, Ligris K, et al. Stress-induced bladder mast cell activation: implications for interstitial cystitis. J Urol 1997; 157: 669-72
79. Ripoll E, Mahowald D. Hatha Yoga therapy management of urologic disorders. World J Urol 2002; 20: 306-9
80. Whitmore KE. Complementary and alternative therapies as treatment approaches for interstitial cystitis. Rev Urol 2002; 4 Suppl.: S28-35
81. Bologna RA, Gomelsky A, Lukban JC, et al. The efficacy of calcium glycerophosphate in the prevention of food-related flares in interstitial cystitis. Urology 2001; 57 Suppl. 1: 119-20
82. Korting GE, Smith SD, Wheeler MA, et al. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. J Urol 1999; 161: 558-65
83. Parsons CL, Benson G, Childs SJ, et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. J Urol 1993; 150: 845-8
84. Mulholland SG, Hanno P, Parsons CL, et al. Pentosan polysulfate sodium for therapy of interstitial cystitis: a double-blind placebo-controlled clinical study. Urology 1990; 35: 552-8
85. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987; 138: 513-6
86. Holm-Bentzen M, Jacobsen F, Nerstrom B, et al. A prospective double-blind clinically controlled multicenter trial of sodium pentosanpolysulfate in the treatment of interstitial cystitis and related painful bladder disease. J Urol 1987; 138: 503-7
87. Sant GR, Propert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003; 170: 810-5
88. Hwang P, Auclair B, Beechinor D, et al. Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. Urology 1997; 50: 39-43
89. Chiang G, Patra P, Letourneau R, et al. Pentosanpolysulfate (Elmiron) is a potent inhibitor of mast cell histamine secretion. Adv Exp Med Biol 2003; 539 (Pt B): 713-29
90. Erickson DR, Sheykhnazari M, Bhavanandam VP. Molecular size affects urine excretion of pentosan polysulfate. J Urol 2006; 175: 1143-7
91. Simon M, McClanahan RH, Shah JF, et al. Metabolism of [3H] pentosan polysulfate sodium (PPS) in healthy human volunteers. Xenobiotica 2005; 35: 775-84
92. Jepsen JV, Sall M, Rhodes PR, et al. Long-term experience with pentosan polysulfate in interstitial cystitis. Urology 1999; 53: 381-7

93. Nickel JC, Barkin J, Forrest J, et al. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. Urology 2005; 65: 654-8
94. Theoharides TC, Sant GR. Hydroxyzine therapy for interstitial cystitis. Urology 1997; 49 Suppl. 5A: 108-10
95. Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder syndrome: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 2001; 87: 207-12
96. Van Ophoven A, Pokupic S, Heinecke H, et al. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004; 172: 533-6
97. Sairanen J, Tammela TL, Leppilahti M, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 2005; 174: 2235-8
98. Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol 2004; 171: 2138-41
99. Davis EL, El Khoudary SR, Talbott EO, et al. Safety and efficacy of the use of intravesical and oral pentosan polysulfate sodium for interstitial cystitis: a randomized double-blind clinical trial. J Urol 2008; 179: 177-85
100. Parsons CL. Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology 2005; 65: 45-8
101. Welk BK, Teichman JMH. Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. Urology 2008; 71: 67-70
102. Mayer R, Propert KJ, Peters KM, et al. A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol 2005; 173: 1186-91
103. Peeker R, Haghsheno MA, Holmang S, et al. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. J Urol 2000; 164: 1912-5
104. Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/interstitial cystitis. Cochrane Database Syst Rev 2007 Oct 17; (4): CD006113
105. Parkin J, Chea C, Sant GR. Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis: a practical approach. Urology 1997; 49 Suppl. 5A: 105-7
106. Giannantoni A, Porena M, Costantini E, et al. A toxin intravesical injection in patients with painful bladder syndrome: 1-year follow up. J Urol 2008; 179: 1031-4
107. Nickel JC, Wyllie MG, Henry RA. Intravesical alkalized lidocaine (PSD597) offers immediate and sustained relief from the symptoms of interstitial cystitis/painful bladder syndrome (IC/PBS): results of a phase II multi-centre placebo-controlled trial [abstract no. 180]. J Urol 2008; 179 Suppl.: 63
108. Henry R, Patterson L, Avery N, et al. Absorption of alkalinized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. J Urol 2001; 165: 1900-3
109. Welk BK, Teichman JMH. Female sexual function improves in treated interstitial cystitis patients [abstract no. 171]. J Urol 2008; 179 (Suppl.): 60
110. Bergman A, Karram M, Bhatia NN. Urethral syndrome: a comparison of different treatment modalities. J Reprod Med 1989; 34: 157-60
111. Lemack GE, Foster B, Zimmern PE. Urethral dilation in women: a questionnaire-based analysis of practice patterns. Urology 1999; 54: 37-43
112. Immergut M, Culp D, Flocks RH. The urethral caliber in normal female children. J Urol 1967; 97: 693-5
113. Shear S, Mayer R. Development of glomerulations in younger women with interstitial cystitis. Urology 2006; 68: 253-6
114. Mattox TF. Interstitial cystitis in adolescents and children: a review. J Pediatr Adolesc Gynecol 2004; 17: 7-11
115. Ratner V. Current controversies that adversely effect interstitial cystitis patients. Urology 2001; 57 Suppl. 6A: 89-94
116. Park JM. Is interstitial cystitis an underdiagnosed problem in children? A diagnostic and therapeutic dilemma. Urology 2001; 57 Suppl. 6A: 30-1
117. Bloom DA, Seeley WW, Rithcey ML, et al. Toilet habits and continence in children: an opportunity sampling in search of normal parameters. J Urol 1993; 149: 1087-90
118. Parsons CL. Interstitial cystitis: clinical manifestations and diagnostic criteria in over 200 cases. Neurourol Urodyn 1990; 9: 241-50
119. Propert KJ, Schaefter AJ, Brensinger CL, et al. A prospective study of interstitial cystitis: results of a longitudinal follow up of the Inerstitial Cystitis Data Base Cohort. J Urol 2000; 163: 1434-9
120. Sensirivatana R, Watana D, Sornmani W, et al. Diagnostic study of urinary frequency in children. Urology 1987; 30: 50-2
121. Walker J, Rickwood AMK. Daytime urinary frequency in children. BMJ 1988; 297: 455
122. Koff SA, Byard MA. The daytime urinary frequency syndrome of childhood. J Urol 1988; 140: 1280-1
123. Corigliano T, Renella R, Robbiani A, et al. Isolated extraordinary daytime urinary frequency of childhood: a case series of 26 children in Switzerland. Acta Paediatr 2007; 96: 1347-9
124. Curran MJ, Kaefer M, Peters C, et al. The overactive bladder in childhood: long-term results with conservative management. J Urol 2000; 163: 574-7
125. Saedi NA, Schulman SL. Natural history of voiding dysfunction. Pedi Nephrol 2003; 18: 894-7
126. Schuster GA. Interstitial cystitis in children: not a rare entity [abstract]. Urology 2001; 57 Suppl. 6A: 107
127. Fisher RE, Tanagho EA, Lyon RP, et al. Urethral calibration in newborn girls. J Urol 1969; 102: 67-9
128. Metwalli AR, Cheng EY, Kropp BP, et al. The practice of urethral dilation for voiding dysfunction among fellows of the Section on Urology of the American Academy of Pediatrics. J Urol 2002; 168: 1764-7
129. National Toxicology Program Public Health Services, National Institutes of Health, US Department of Health

and Human Services. NTP technical report on the toxicology and carcinogenesis studies of Elmiron (Case no. 37319-17-8) in F344/N rats and B6C3F1 mice (Gavage studies). Natl Toxicol Program Tech Repro Ser 2004; 512: 7-289

130. Scarapa MD, Mori N, Canning BJ. Gastroesophageal reflux disease in children with asthma: treatment implications. Paeditr Drugs 2005; 7: 777-86

131. Selo-Ojeme DO, Paranjothy S, Onwude JL. Interstitial cystitis coexisting with vulvar vestibulitis in a 4-year-old girl. Int Urogynecol J 2002; 13: 261-2

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