Anorectal and Pelvic Pain

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Abstract

Although pelvic pain is a symptom of several structural anorectal and pelvic disorders (eg, anal fissure, endometriosis, and pelvic inflammatory disease), this comprehensive review will focus on the 3 most common nonstructural, or functional, disorders associated with pelvic pain: functional anorectal pain (ie, levator ani syndrome, unspecified anorectal pain, and proctalgia fugax), interstitial cystitis/bladder pain syndrome, and chronic prostatitis/chronic pelvic pain syndrome. The first 2 conditions occur in both sexes, while the latter occurs only in men. They are defined by symptoms, supplemented with levator tenderness (levator ani syndrome) and bladder mucosal inflammation (interstitial cystitis). Although distinct, these conditions share several similarities, including associations with dysfunctional voiding or defecation, comorbid conditions (eg, fibromyalgia, depression), impaired quality of life, and increased health care utilization. Several factors, including pelvic floor muscle tension, peripheral inflammation, peripheral and central sensitization, and psychosocial factors, have been implicated in the pathogenesis. The management is tailored to symptoms, is partly supported by clinical trials, and includes multidisciplinary approaches such as lifestyle modifications and pharmacological, behavioral, and physical therapy. Opioids should be avoided, and surgical treatment has a limited role, primarily in refractory interstitial cystitis.

Anorectal and pelvic pain is a manifestation of several structural and functional disorders affecting the anus and rectum, urinary bladder, reproductive system, and pelvic floor musculature and its innervation. In contrast to structural diseases such as endometriosis, the pelvic pain in functional disorders cannot be explained by a structural or other specified pathologic process. Functional disorders are classified into anorectal (eg, proctalgia fugax, levator ani syndrome, and unspecified anorectal pain), bladder (eg, interstitial cystitis [IC]/bladder pain syndrome [BPS]), and prostate syndromes (eg, chronic prostatitis [CP]/chronic pelvic pain syndrome [CPPS]). Interstitial cystitis/bladder pain syndrome is primarily diagnosed in women, whereas CP/CPPS is a diagnosis exclusive to men. Historically, these conditions have been regarded as distinct, and this review discusses them separately. However, more recent reviews emphasize the shared features between IC/BPS and CP/CPPS, which is captured by the term urologic chronic pelvic pain syndromes. These urogynecologic syndromes also share several features with anorectal pain syndromes (Tables 1 and 2).

Expert panels have relied on evidence, supplemented by the Delphi process, to develop diagnostic criteria and treatment guidelines for these disorders. The aim of this review is to summarize the evidence on the epidemiology, natural history, pathophysiology, diagnosis, and management of these conditions. This review, which is updated from an earlier review, incorporates the most recent recommendations, including the Rome criteria for anorectal disorders published in May 2016, the American Urological Association guidelines for IC/BPS from 2015, and a Prostatitis Expert Reference Group document on CP/CPPS from 2015.

METHODS

For this review, we searched Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R), and Ovid EMBASE. Although the topics overlapped, each was searched separately, and building on previous systematic reviews, the searches extended back to 1995 for anorectal and mixed pain syndromes, 2008 for chronic pain, and 2014 for chronic prostatitis. The Medical Subject Headings of the US National
Library of Medicine (MeSH) term pelvic pain was expanded to include dysmenorrhea, piriformis syndrome, and pelvic girdle pain combined with either MeSH terms chronic disease or chronic pain. This concept was also searched by the term chronic appearing within 3 words adjacent to pelvic pain as text words. Chronic prostatitis was similarly searched using MeSH terms prostatitis and chronic pain or chronic appearing within 2 words of prostatitis. For anorectal pain, the only MeSH terms were quite general; the search used text words levator ani, proctalgia fugax, puborectal myalgia, coccygodynia, and anorectal within 2 words of pain*. The strategies were then translated in the EMBASE vocabulary EMTREE, or text words, and run. Duplicates were removed, giving precedence to the MEDLINE results.

**Epidemiology**
In the only population-based survey, which was conducted in a sample of US householders in 1990, the prevalence of anorectal pain, levator ani syndrome, and proctalgia fugax, as determined by a symptom-based questionnaire (Table 3), was 11.6% (11.1% in men and 12.1% in women), 6.6% (5.7% in men and 7.4% in women), and 8% (7.5% in men and 8.3% in women), respectively. The prevalence of anorectal pain was higher in those younger than 45 years (14% vs 9% in those ≥45 years). Similar trends were observed for levator ani syndrome and proctalgia fugax. Approximately 8.3% with functional anorectal pain, 11.5% with levator ani syndrome, and 8.4% with proctalgia fugax reported they were currently too sick to work or go to school.

**Pathophysiology**
In levator ani syndrome, uncontrolled studies have implicated a role for pelvic floor muscle spasm, increased anal resting pressures, and dyssynergic defecation, which is characterized by anorectal incoordination during defecation and often improves with biofeedback therapy (Figure 1). In proctalgia fugax, the short duration and sporadic, infrequent pain episodes have limited the identification of physiologic mechanisms. Excessive colonic and anal smooth muscle contraction have been observed. Hereditary proctalgia fugax is associated with constipation and hypertrophy of the internal anal sphincter.

**Clinical Features**
Among patients with constant or recurrent rectal pain, the pain is (ie, levator ani syndrome) or is not (ie, unspecified anorectal pain) associated with tenderness on palpation of the levator ani muscle. Whereas unspecified anorectal pain is not. By contrast, the pain in proctalgia fugax is brief (ie, lasts for seconds to minutes) and occurs infrequently (ie, once a month or less often) (Table 3).

**TABLE 1. Cardinal Features of Chronic Functional Anorectal and Urogynecologic Disorders**
- Disorders are diagnosed by symptoms, supplemented by objective findings in interstitial cystitis and levator ani syndrome
- Predominant symptom is discomfort or pain; patients may also have dysfunctional voiding or defecation
- Frequently associated with a broad range of psychosocial issues (eg, anxiety and depression)
- Negative effects on quality of life
- Pathophysiology is poorly understood
- Therapy is largely symptomatic, guided by the primary symptom(s) and their severity, and includes pharmacotherapy, physical therapy, and psychosocial therapy
are other terms used to describe chronic rather than brief pain (ie, proctalgia fugax).

Proctalgia fugax is characterized by recurrent episodes of pain localized to the rectum and unrelated to defecation. In a series of 54 patients, attacks generally occurred suddenly, during the day or at night, and once a month.24 In some patients, attacks were precipitated by stressful life events or anxiety.25 The nonradiating cramp, spasm, or stabbing pain without concomitant symptoms lasted, on average, for 15 minutes and dissipated spontaneously.26

**Management**

Diagnostic tests to exclude a structural disorder and to identify a defecatory disorder should be performed as necessary (Figure 2).28 Anoscopy may be necessary to identify anal fissures and hemorrhoids; the examination should be performed with anesthesia for patients who have severe pain. Chronic proctosigmoiditis, which is generally due to inflammatory bowel disease and, rarely, ischemia, can be identified by flexible sigmoidoscopy. Pelvic magnetic resonance imaging may be necessary to identify perirectal abscesses or fistulae. In addition to features of a defecatory disorder (eg, impaired anal relaxation, paradoxical contraction of the puborectalis, or impaired rectal evacuation),28,29 dynamic imaging (eg, magnetic resonance or barium proctography) may also identify other abnormalities (eg, high-grade internal rectal prolapse), which may reflect incidental findings or excessive straining rather than a cause of chronic pain.30,31 Except for 2 controlled studies, most therapeutic trials for chronic intractable anorectal pain have been uncontrolled. One controlled trial randomly

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<table>
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<tr>
<th>TABLE 2. Clinical Features of Functional and Chronic Anorectal and Pelvic Pain Disorders</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Average age</td>
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<tr>
<td>Sex</td>
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<td>Pain characteristics</td>
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<td>Associated symptoms</td>
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<td>Physical examination</td>
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<tr>
<td>Internal pelvic tender points</td>
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<td>External pelvic tender points</td>
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*a An increase in discomfort with bladder filling and relief with voiding.
*b Herniated lumbar disk, hysterectomy, or low anterior resection.
*c No urge urinary incontinence and no response to overactive bladder treatment (eg, anticholinergics).
*d Asymmetric (left side greater than right side) and predictor of successful biofeedback therapy.
*e Extreme tenderness on gentle palpation of the prostate should raise suspicion for acute bacterial prostatitis or even a prostatic abscess.
assigned 157 patients with chronic proctalgia to receive 9 sessions of electrical stimulation, digital massage of the levator ani and warm sitz baths, or pelvic floor biofeedback plus psychological counseling. The randomization was stratified on the basis of tenderness on palpation of the pelvic floor muscles during a digital rectal examination. Among patients who reported such tenderness, 87% reported adequate relief of rectal pain after biofeedback therapy, 45% after electrical stimulation, and 22% after massage. This improvement was maintained 12 months later. Impaired pelvic floor relaxation and rectal balloon expulsion also predicted a response to biofeedback therapy. Biofeedback therapy improved anorectal coordination during evacuation. By contrast, patients who did not report tenderness on palpation did not respond to any of these treatments. In another controlled study, injections of botulinum toxin into the levator ani muscle administered twice over 3 months were not superior to placebo in 12 patients with levator ani syndrome.

An uncontrolled study observed that sitz baths improved chronic anorectal pain. Besides counterirritation, hot water may reduce anal pressures. In one study, a combination of approaches (ie, massage, sitz baths, muscle relaxants, and diathermy) was effective in 68% of 316 patients with levator ani syndrome. In another uncontrolled study of 158 patients with chronic anorectal pain, symptoms improved after biofeedback therapy (17/29 patients [58.6%]), tricyclic antidepressants (10/26 patients [38.5%]), botulinum toxin injection (5/9 patients [55.6%]), and sacral nerve stimulation (2/3 patients [66.7%]).

The efficacy of another method, ultrasound-guided injection of either local anesthetic or alcohol for pelvic nerves (eg, pudendal nerve), has not been proved. Three small uncontrolled case series with a total of fewer than 30 patients suggested that sacral nerve stimulation (SNS) may benefit some patients. In our opinion, SNS should not be used to manage levator ani syndrome outside of clinical trials.

We have evaluated patients with refractory anorectal pain who had persistent symptoms despite surgical interruption of the puborectalis muscle. This procedure is of unproven benefit and may lead to fecal incontinence. Likewise, there is little evidence that surgical treatment of internal rectal prolapse or other incidental abnormalities observed with dynamic magnetic resonance proctography will improve chronic anorectal pain. Rather, patients with refractory pain, most of whom, in our experience, have psychosocial comorbid conditions, should be referred to a multidisciplinary pain rehabilitation program. These programs integrate physical therapy, occupational therapy, and cognitive-behavioral therapy in an intensive, interdisciplinary, outpatient setting. The emphasis is on physical reconditioning and elimination of medications for pain (eg, opioids) and other symptoms (eg, benzodiazepines), along with activity management and behavior therapy. Most pain rehabilitation centers offer daily treatment for 2 to 4 weeks. Patients who benefit from this approach do so because of a change in their behavior, beliefs, and physical status. The efficacy of these programs has been reported for chronic pain, including chronic abdominal pain, but not specifically for chronic pelvic pain.

For most patients with proctalgia fugax, the emphasis is on reassurance and explanation. The episodes of pain are so brief and infrequent that remedial treatment is impractical and prevention is not feasible. The inhaled β2-adrenergic agonist salbutamol is more effective than placebo for shortening the duration of episodes of proctalgia.

<table>
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<tr>
<th>Condition</th>
<th>Questionnaire</th>
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<tr>
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<td>American Urological Association Symptom Index</td>
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<tr>
<td>Chronic prostatitis/chronic pelvic pain syndrome</td>
<td>National Institutes of Health Chronic Prostatitis Symptom Index, International Prostate Symptom Score, Urinary, Psychosocial, Organ specific, Infection, Neurologic/systemic, and Tenderness system</td>
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<tr>
<td>Interstitial cystitis and bladder pain syndrome</td>
<td>Interstitial Cystitis Symptom Index</td>
</tr>
<tr>
<td>Functional anorectal pain</td>
<td>Rome IV Questionnaire</td>
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<tr>
<td>Psychosocial assessment</td>
<td>Patient Health Questionnaire-2, Patient Health Questionnaire-9, Generalized Anxiety Disorder 7-Item Scale, Hospital Anxiety and Depression Scale</td>
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CHRONIC PROSTATITIS AND CHRONIC PELVIC PAIN SYNDROME

Definition
A syndrome exclusive to men, CP/CPPS is “characterized by chronic pain in the perineum, tip of the penis, suprapubic region, or scrotum, which is often worsened with voiding or ejaculation, in the absence of an organic disorder.” Chronic prostatitis/chronic pelvic pain syndrome (type III prostatitis in the National Institutes of Health classification) constitutes the vast majority (ie, >90%) of cases of symptomatic prostatitis. Other diagnoses in this classification include acute bacterial prostatitis (type I), chronic bacterial prostatitis (type II), and asymptomatic inflammatory prostatitis (type IV).

Epidemiology
The condition affects men of all ages and has a prevalence of 2% to 10%. Patients with CP/CPPS account for approximately 2 million medical office visits per year in the United States.

Pathophysiology
The pathophysiology of CP/CPPS is unclear. Putative mechanisms are depicted in Figure 1. Historically, CP has been regarded as an infectious disease and treated with antibiotics. The
infection is diagnosed by culturing bacteria from urine or expressed prostatic secretions. However, most bacteria resist cultivation, perhaps because most chronic bacterial infections are associated with a biofilm mode of growth that is difficult to culture.44 In a study of a molecular technique not dependent on cultures, Nichel et al45 observed that the overall species and genus composition differed only in the initial urine stream of patients with urologic CPPS vs controls, with *Burkholderia cenocepacia* overrepresented in those with urologic CPPS. By contrast, midstream or postprostatic massage samples were not significantly different. The absence of microbiota does not exclude the possibility that CPPS is initiated by infection, although chronic inflammation and pain may persist after the infection has been cleared.46 Prostate biopsies reveal inflammation in 33% of patients with CP/CPPS.47 Neurogenic processes, autoimmune injury, and mast cells may contribute to inflammation. However, this inflammation does not correlate with the severity of pain.48 The concentration of nerve growth factor—which is involved in nerve function, regrowth after nerve injury, and neurogenic inflammation—in expressed prostatic secretions is higher in patients with CP/CPPS than in asymptomatic controls. Also, nerve growth factor concentrations are correlated with the severity of pain.49 In some patients, there is evidence of an autoimmune process.46 Expressed prostatic secretions in men with CPPS have increased mast cell tryptase and nerve growth factor.50 Peripheral inflammation may lead to central sensitization, which may perpetuate increased visceral sensitivity.51 Psychological stress is common52 and may also increase visceral sensitivity.53

**Clinical Features**

Chronic prostatitis/chronic pelvic pain syndrome is associated with various clinical features, such as urogenital pain, urinary symptoms, sexual dysfunction, and psychosocial symptoms (Table 2). Perineal pain is most
frequent; other locations are the testes, pubis, and penis. Between 39% and 68% of patients have lower urinary tract symptoms. A meta-analysis observed an increased risk (pooled odds ratio, 3.02; 95% CI, 2.18-4.17) of erectile dysfunction in patients with CP/CPPS.54

A large case-control study found that the urological chronic pain syndromes (ie, CP/CPPS and IC/BPS) were associated with not only negative effects but also a broader spectrum of psychosocial disturbances, including “higher levels of current and lifetime stress, poorer illness coping, increased self-report of cognitive deficits, and more widespread pain symptoms compared with sex- and education-matched” healthy men and women.55 Case patients also had greater difficulties with sleep and functioning in sexual relationships. Indeed, the QoL in patients with CP/CPPS is similar to that of patients who have had myocardial infarction or have Crohn disease.56

Between 22% and 31% of patients with CP/CPPS have symptoms of irritable bowel syndrome.6 When compared with age-matched controls, men who have CP/CPPS have a higher incidence of cardiovascular disease, neurologic disease, and sinusitis.57

The physical examination should include palpation of pelvic muscles (which may be tender and may not contract and/or relax appropriately), the bladder and prostate (which may be enlarged), and the anal sphincter (which may be weak and/or not relax adequately).

Diagnostic Tests
A history and physical examination (including digital rectal examination), urinalysis, and urine cultures should be performed. A pre- and post-prostate massage urine test is as sensitive and specific as the 4-glass test for diagnosing chronic bacterial prostatitis.58 Other tests for consideration include prostate ultrasonography, urethral swab, urodynamic studies, and prostate-specific antigen measurement.59 Very rarely, perineal pain may be a manifestation of a lumbosacral spinal cord lesion.59 Spinal imaging should be considered if other neurologic symptoms or signs are present.

Management
Therapeutic options are of variable efficacy (Table 4).60-67 Because the clinical features are heterogeneous and vary among patients, it has been suggested that “one size may not fit all.” Rather, therapy individualized to the specific symptom(s) may be preferable.68 The UPOINT (Urinary, Psychosocial, Organ specific, Infection, Neurological/systemic, and Tenderness) scoring system includes 6 domains: (1) irritative or obstructive urinary symptoms, (2) psychosocial issues, (3) organ-specific (bladder or prostate) symptoms (pain associated with bladder filling and relieved with voiding, prostate tenderness, and leukocytosis in expressed prostatic specimens), (4) infections (positive prostatic fluid culture results in the absence of urinary tract infection, urethritis), (5) neurologic/systemic symptoms (pain outside the pelvis, systemic pain syndromes [eg, fibromyalgia, irritable bowel syndrome]), and (6) tenderness (pelvic floor spasm, muscle trigger points in the abdomen/pelvis).69 Limited evidence from an uncontrolled prospective study of 100 patients in which management was guided by the UPOINT assessment indicated that symptoms improved significantly in 84% of patients and by 50% or more in 51%.69 Although this study was not controlled, these response rates were comparable to or better than those observed in other controlled trials with monotherapy.

Supported by strong evidence, first-line approaches include antibiotics for infections and α-blockers or anticholinergic medications for urinary symptoms60 (Table 4). Simple analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs), followed if necessary by neuromodulators, tricyclic antidepressants (eg, nortriptyline, amitriptyline), or serotonin-norepinephrine reuptake inhibitors (eg, duloxetine) should be considered for pain. Phytotherapy (eg, rye pollen extract and the bioflavonoid quercetin) also improved pain and QoL in small controlled clinical trials.60-70 For erectile dysfunction, 5α-reductase inhibitors are recommended in patients with coexistent benign prostatic enlargement.

Pelvic floor physical therapy can improve overall symptoms and sexual dysfunction.71 In a small study of 29 patients, greater than 50% improvement in pain scores was observed with physical therapy in 59% of patients and with levator-directed trigger-point injections in 58% of patients.72 The
high prevalence and severity of psychosocial issues in patients with urologic chronic pain syndromes underscores the need for appropriate pharmacotherapy, counseling, and/or cognitive-behavioral therapy. These modalities are often integrated into multidisciplinary programs that incorporate physical therapy, particularly for patients whose symptoms are refractory to other approaches. However, we believe that these approaches are underutilized in clinical practice. A meta-analysis of 7 trials involving 471 patients observed that acupuncture was superior to sham acupuncture in improving symptoms and QoL. Microwave thermotherapy or transurethral needle ablation of the prostate have limited efficacy. There is insufficient evidence to gauge the benefit of SNS for refractory CP/CPPS. There is also little evidence to support the use of other surgical techniques, even for refractory CP/CPPS (Table 4).
INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Definition
In 1987, the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis proposed diagnostic criteria for clinical trials. However, these criteria are too restrictive for daily use and have been estimated to miss 60% of patients with BPS. In 2009, the Society for Urodynamics and Female Urology defined IC/BPS as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms (eg, urinary frequency), and lasting more than 6 weeks in the absence of infection or other identifiable causes. Some patients with BPS have IC, which is characterized by symptoms of BPS and vesical abnormalities (ie, mucosal ulcerations [Hunner ulcers]), punctate hemorrhages (glomerulations) after bladder hydrodistention, and an increased number of detrusor mast cells. This definition was also adopted by the updated guidelines issued by the American Urological Association in 2015.

Epidemiology
As detailed elsewhere, the prevalence of IC/BPS depends on the criteria and the methods (ie, self-report, questionnaires, or administrative billing data) used to diagnose it. The most recent questionnaire-based study in US adult women reported a prevalence of 2.7% using highly specific criteria and 6.53% using highly sensitive criteria, which translates to between approximately 3.3 and 7.9 million women. Only 9.7% of these women had an actual diagnosis of IC/BPS. Among adult men, symptoms of IC/BPS are also common, with an estimated prevalence of 2.9% to 4.2%. However, the condition may be underdiagnosed. In the RAND Interstitial Cystitis Epidemiology male study, 1.8% of adult men had CP/CPPS, and approximately 17% had both IC/BPS and CP/CPPS.

The economic impact of IC/BPS has been summarized elsewhere. Among a cohort of 239 patients in a managed care setting, the mean cost of IC was $6614, including $1572 for prescription medications and $3463 for outpatient medical services. Among women with IC/BPS, 19% lost wages, with a mean annual cost of $4216.

Pathophysiology
Current concepts derived largely from in vitro and animal studies support the following framework (Figure 1). Normally, the urothelium is covered by a protective layer of glycosaminoglycans (eg, chondroitin sulfate, hyaluronic sodium, glycoproteins, and mucins). Damage to this layer may increase urothelial permeability and predispose patients to chronic diffusion of irritants across the urothelium, mast cell activation, and neurogenic inflammation. Bladder mast cells are increased by a factor of 6- to 10-fold in classic/ulcerative IC compared with a 2-fold increase in nonulcerative IC. Degranulation of mast cells activates capsaicin-sensitive nerve fibers that release substance P and other neuropeptides, which cause cell damage. Prolonged activation of mast cells and capsaicin-sensitive nerve fibers can also cause neurogenic up-regulation. Mediators (eg, glutamate, substance P, and calcitonin gene–related peptide) that are released from the central terminals of primary afferent fibers in the dorsal horn of the spinal cord cause central sensitization, resulting in hypersensitivity to nonpainful and normally painful stimuli. Peripheral mechanisms damage bladder muscle and cause bladder fibrosis.

The primary insult causing IC/BPS is unknown. A role for bacterial infection and autoimmunity has been proposed but is not widely accepted. Patients with IC have reported frequent childhood bladder infections and urinary urgency in adolescence. Environmental factors such as stress and certain foods and drinks (eg, alcohol, citrus fruits, coffee) can aggravate pain. Supporting a role for genetic factors, the prevalence of IC is 17 times greater in first-degree relatives of patients with IC than in the general population and is also greater in monozygotic than in dizygotic twins.

A case-control study found that the diagnosis of 6 nonbladder syndromes (eg, fibromyalgia-chronic widespread pain, irritable bowel syndrome, and panic disorder) preceded the diagnosis of IC/BPS. These findings were broadly confirmed in a subsequent report. There are 3 possible
explanations for such associations: (1) that the nonbladder and bladder syndromes share genetic or environmental risk factors, (2) that the syndrome is a risk factor for IC/BPS, or (3) that the syndrome and IC/BPS are different manifestations of the same pathophysiologic process or disease. Prospective studies are necessary to confirm these associations.

**Clinical Features**
Initially, patients with IC/BPS may report only one symptom such as dysuria, frequency, or pain (Table 2). Subsequently, the typical symptoms develop, such as pelvic pain, pressure, or discomfort and daytime urinary frequency (>10 times) or urgency, which is due to pain, pressure, or discomfort and not due to fear of wetting. Symptoms may flare for several hours to weeks. Symptoms are similar in men and women.

Other coexistent conditions include irritable bowel syndrome, anxiety and depression, fibromyalgia, chronic fatigue syndrome, chronic headache, dysmenorrhea, and vulvodynia. Indeed, the UPOINT system can also be used for IC/BPS. Women with IC undergo significantly more pelvic operations (eg, hysterectomy) than controls. Interstitial cystitis/bladder pain syndrome can profoundly impair psychosocial functioning and QoL. The effect on QoL is as severe as that in rheumatoid arthritis and end-stage renal disease. Women with IC/BPS have significantly more pain, sleep dysfunction, catastrophizing, depression, anxiety, difficulty with social functions, and sexual dysfunction than women without IC/BPS. Sexual dysfunction is moderate to severe, secondary to the pain in IC/BPS, and is the primary predictor of poor QoL.

Physical examination may disclose tenderness of the pelvic muscles, bladder, urethra, or external genitalia; palpation-induced abdominal tenderness; pelvic asymmetry; and pelvic floor dysfunctions, which may be manifested as an inability to maintain pelvic relaxation. An occult neurologic problem and occult urinary retention should be excluded with a neurologic examination and assessment of the postvoid residual urine volume, respectively.

**Diagnostic Tests**
At baseline, the intensity of pain should be evaluated with standardized instruments (eg, O’Leary-Sant interstitial cystitis symptom/problem index or a 10-point Likert scale). At a minimum, voiding symptoms should be assessed with a 1-day voiding diary, which is as useful as a 3-day voiding diary. These assessments not only help establish the diagnosis but also provide a baseline against which the response to treatment can be evaluated. Alternative diagnoses should be sought in patients who have very low voiding frequencies or high voided volumes instead of a low-volume/frequent-voiding pattern. A urinary tract infection should be excluded with urinalysis and a urine culture in all patients. Urine cytology should be assessed in patients with microhematuria and in smokers, who have a greater risk of bladder cancer. Cystoscopy and urodynamic studies are only required if the diagnosis is in doubt or the information might guide therapy. Cystoscopy may reveal Hunner ulcers, which are inflammatory-appearing lesions seen in IC/BPS, or glomerulations (ie, pinpoint submucosal petechial hemorrhages), which are consistent with IC/BPS but are also seen in other conditions (eg, chronic undifferentiated pelvic pain) that mimic or coexist with IC/BPS. Cystoscopy can also identify bladder cancer or stones and urethral diverticula. During cystoscopy, hydrodistention is not routinely necessary to diagnose IC/BPS. Urodynamic testing is useful in patients with suspected outlet obstruction or poor detrusor contractility and in patients who are refractory to initial therapy. Urodynamic testing may reveal pain during bladder filling and/or features of voiding dysfunction (eg, bladder outlet obstruction, detrusor overactivity, or pelvic floor dysfunction). However, there are no urodynamic features specific for IC/BPS. Assessment of permeability by measuring the intravesicular potassium level is prone to false-positive and false-negative results and is not recommended for diagnosis of IC.

**Differential Diagnosis**
Endometriosis is also associated with pelvic pain and urinary symptoms. Among 1000 patients with endometriosis, pelvic pain (68%),
dysmenorrhea (79%), and dyspareunia (45%) were the most common presenting symptoms.96,97 Because the response to hormonal treatment does not reliably predict endometriosis, laparoscopy with biopsy of suspected lesions is necessary for diagnosing endometriosis.98 The abnormalities on cystoscopy described previously may favor a diagnosis of IC.

Overactive bladder and IC/BPS share several symptoms (ie, urinary urgency, frequency, and nocturia). Severe pelvic pain and dyspareunia suggest IC/BPS, whereas urge urinary incontinence suggests overactive bladder syndrome.99 Interstitial cystitis/bladder pain syndrome should be considered in patients with symptoms of refractory overactive bladder.99 During urodynamic studies, patients with IC/BPS are more likely to have hypersensitivity and lower capacity during filling cystometry, but detrusor overactivity is more common in overactive bladder syndrome.100,101 However, these urodynamic findings do not necessarily help distinguish between these 2 diseases.

Patients with vulvodynia generally report vulvar burning and dyspareunia but not urinary symptoms.96 Coccygodynia presents as pain arising in or around the coccyx that is usually triggered by prolonged sitting on hard surfaces.102 The pain may be preceded by or associated with trauma, childbirth, or lumbar disk degeneration. Patients with coccygodynia have tenderness on palpation or manipulation of the coccyx.

Management

Patients with IC/BPS should be educated about possible underlying causes and treatment options (Table 5).103-117 Lifestyle modifications include avoiding factors that may precipitate symptoms (eg, excessive fluid intake, coffee, citrus products, sexual intercourse, and tight-fitting clothing).13 Application of local heat or cold over the bladder or perineum may also be useful.

Thereafter, there are several options, albeit supported by variable, generally limited evidence (Table 4). Analgesics and neuromodulating agents are recommended for alleviating pain; opioids should be avoided.5 Initial oral pharmacological options include pentosan polysulfate sodium (PPS), hydroxyzine (a histamine 1 receptor antagonist), tricyclic antidepressants, and cimetidine (a histamine 2 receptor antagonist). Pentosan polysulfate sodium is a heparin-like sulfated polysaccharide that is similar to glycosaminoglycans, is purported to repair the damaged glycosaminoglycan layer lining the urothelium, and improves decreased urothelial permeability. In vitro data suggest that PPS also has anti-inflammatory effects. In randomized, placebo-controlled clinical trials of IC/BPS, the response rates were approximately 30% for PPS and 15% for placebo.118 Pentosan polysulfate sodium is the only oral medication approved by the US Food and Drug Administration for treatment of IC/BPS. Systematic reviews based on limited data have revealed modest benefits of PPS, amitriptyline, and hydroxyzine compared with placebo. When oral therapy is insufficient, intravesical instillation with dimethyl sulfoxide (approved by the US Food and Drug Administration), heparin, and lidocaine or cystoscopy with hydrodistention should be considered. At cystoscopy, a Hunner ulcer may be fulgurated with laser or electrocautery.

Intradetrusor administration of botulinum toxin type A inhibits the release of neurotransmitters (acetylcholine, norepinephrine, nerve growth factor, adenosine triphosphate, substance P, and calcitonin gene–related peptide) from the urothelium and in nerve fibers. Botulinum toxin type A also inhibits sensory receptors in suburothelial nerve fibers.119 By inhibiting this neuroplasticity, botulinum toxin type A might reduce pain and urgency. Indeed, at 3 months, symptoms were moderately or markedly improved in 72% of patients after intradetrusor botulinum toxin type A injection (100 U) and bladder hydrodistention, compared with only 48% after hydrodistention alone, and all differences were significant; all patients were also treated with PPS.113 However, responses waned over time; by 2 years, corresponding responses were 21% and 17% for the combined group and hydrodistention alone, respectively. Bladder capacity and other cystometric variables improved with botulinum toxin and hydrodistention but not after hydrodistention alone. Cyclosporine may be beneficial in patients whose symptoms are refractory to the aforementioned approaches, especially in patients with Hunner ulcers or active bladder inflammation; however, adverse effects are common.108
Although the evidence is limited, SNS should be considered before bladder augmentation or cystectomy with urinary diversion in patients whose symptoms are refractory to medical treatment. In the largest series of 78 patients with BPS and cystoscopic evidence of glomerulation or ulcer, 44 (56%) reported significant improvement after temporary stimulation, and 41 proceeded to permanent SNS. With permanent SNS, 23 of 33 patients who retained the implant (70%) reported very good and 10 (30%) reported good improvement. Various reasons (eg, poor outcomes, pain) prompted explantation of the device in 28% of patients. Finally, a bladder operation may be necessary in patients with symptoms refractory to medical therapy and SNS and a small bladder.\(^{117,120,121}\)

**CONCLUSION**

The functional anorectal and urogynecologic disorders associated with pelvic pain are defined by symptoms, along with levator tenderness (levator ani syndrome) and bladder mucosal inflammation (IC). Common to these conditions are associations with dysfunctional voiding or defecation, comorbid conditions (eg, fibromyalgia, depression), impaired QoL,

### TABLE 5. Treatment of Interstitial Cystitis/Bladder Pain Syndrome\(^a\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Evidence strength(^b)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>NSAIDs</td>
<td>Expert opinion</td>
<td>Consider multimodality therapy. Avoid opioids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(^B)(^{103})</td>
<td>Restores epithelial permeability barrier</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Only oral therapy approved by the FDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Main adverse effect is sedation</td>
</tr>
<tr>
<td>Restore epithelial barrier</td>
<td>Pentosan polysulfate sodium</td>
<td>(^C)(^{104})</td>
<td>Potential for drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(^B)(^{105})</td>
<td>May be used in combination with pentosane polysulfate sodium, hydroxyzine(^107)</td>
</tr>
<tr>
<td>Mast cell stabilizers</td>
<td>Hydroxyzine</td>
<td>(^C)(^{105})</td>
<td>Reserve for refractory IC/BPS</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>(^B)(^{106})</td>
<td>Potential for serious adverse effects</td>
</tr>
<tr>
<td>Neuromodulators</td>
<td>Amitriptyline</td>
<td>(^C)(^{108})</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Cyclosporine A</td>
<td>(^C)(^{109})</td>
<td></td>
</tr>
<tr>
<td>Intravesicular therapy</td>
<td>Dimethyl sulfoxide</td>
<td>(^C)(^{110})</td>
<td>Only intravesicular therapy approved by the FDA</td>
</tr>
<tr>
<td>Free radical scavenger</td>
<td></td>
<td></td>
<td>May be administered as a cocktail with heparin, sodium bicarbonate, lidocaine, and corticosteroids(^5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infrequent and minor adverse effects in uncontrolled studies</td>
</tr>
<tr>
<td>Restore bladder barrier</td>
<td>Heparin</td>
<td>(^C)(^{111})</td>
<td>Combination with sodium bicarbonate avoids ionization within urine, thereby increasing ability to penetrate uroepithelium</td>
</tr>
<tr>
<td>Topical anesthetics</td>
<td>Lidocaine</td>
<td>(^C)(^{112})</td>
<td>Generally performed with low pressure (60-80 cm water) and for a short duration (&lt;10 min)</td>
</tr>
<tr>
<td>Hydrodistention of bladder</td>
<td>Low pressure and short duration</td>
<td>(^C)(^{113})</td>
<td></td>
</tr>
<tr>
<td>Bladder fulguration</td>
<td>Laser, electrocautery</td>
<td>(^B)(^{114})</td>
<td>Considered for Hunner ulcers</td>
</tr>
<tr>
<td>Botulinum toxin type A</td>
<td>Intradetrusor injection</td>
<td>(^C)(^{115})</td>
<td>Doses of 100 and 200 U provided comparable relief, but urinary retention was more common after 200 U(^115)</td>
</tr>
<tr>
<td><strong>Surgical procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacral nerve stimulation</td>
<td>Sacral neuromodulation (InterStim; Medtronic, Inc)</td>
<td>(^C)(^{116})</td>
<td>More effective for urinary symptoms than pain</td>
</tr>
<tr>
<td>Bladder operation</td>
<td>Substitution cystoplasty</td>
<td>(^C)(^{117})</td>
<td>Last resort</td>
</tr>
<tr>
<td></td>
<td>Urinary diversion with/without cystectomy</td>
<td></td>
<td>Patients should be informed that pain may persist postoperatively</td>
</tr>
</tbody>
</table>

\(^a\)FDA = US Food and Drug Administration; IC/BPS = interstitial cystitis/bladder pain syndrome; NSAID = nonsteroidal anti-inflammatory drug.

\(^b\)Levels of evidence: A, meta-analysis of well-designed randomized controlled trials; B, at least one well-designed randomized controlled trial; C, at least one well-designed observational study; D, case series.
and increased health care utilization. Diagnostic tests are primarily required, when appropriate, to exclude structural causes of pelvic pain. Multidisciplinary treatment approaches that integrate lifestyle modifications, pharmacotherapy, and behavioral or psychological therapy that are tailored to the symptoms should be considered.

Abbreviations and Acronyms: BPS = bladder pain syndrome; CP = chronic prostatitis; CPPS = chronic pelvic pain syndrome; IC = interstitial cystitis; MeSH = Medical Subject Headings of the US National Library of Medicine; PPS = pentosan polysulfate sodium; QoL = quality of life; SNS = sacral nerve stimulation; UPPOINT = Urinary, Psychosocial, Organ specific, Infection, Neurological/systemic, and Tenderness scoring system

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Potential Competing Interests: Dr Bharucha has received consulting fees from Allergan Plc, Johnson & Johnson Inc, Medspira, Ironwood Pharmaceuticals, Inc, GlaxoSmithKline Inc, National Center for Pelvic Pain Research, Salix Pharmaceutical Inc, he has patented an anorectal pharmaceutical, Inc, National Center for Pelvic Pain Research, Salix Pharmaceuticals, Inc, gIcare Pharmaceuticals, Inc, Ironwood Pharmaceuticals, Inc, gIcare Pharma Inc, consulting fees from Allergan Plc, Johnson & Johnson Inc, NCPH, Medspira, Ironwood Pharmaceuticals, Inc, gIcare Pharmaceuticals, Inc, gIcare Pharma Inc; he has patented an anorectal manometry device with royalties paid to Medspira and has a pending patent for an anorectal manometry probe fixation device licensed to Medtronic Inc.

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The Symposium on Pain Medicine will continue in an upcoming issue.

REFERENCES
ANORECTAL AND PELVIC PAIN


