

Many patients with IC/BPS also have other syndromes, such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and migraine. These syndromes collectively are known as *functional somatic syndromes* (FSSs): chronic conditions in which pain and fatigue are prominent features but laboratory tests and histologic findings are normal. Like IC/BPS, the FSSs often are associated with depression and anxiety. The majority of FSSs affect more women than men, and more than one FSS can affect a single patient. Because of its similar features and comorbidity, IC/BPS sometimes is considered an FSS.

EPIDEMIOLOGY

Contemporary population studies of IC/BPS in the United States indicate a prevalence of 3–6% among women and 2–4% among men. For decades, it was thought that IC/BPS occurred mostly in women. These prevalence findings, however, have generated research aimed at determining the proportion of men who have symptoms usually diagnosed as chronic prostatitis (now known as chronic prostatitis/chronic pelvic pain syndrome) but who actually have IC/BPS.

Among women, the average age at onset of IC/BPS symptoms is the early forties, but the range is from childhood through the early sixties. Risk factors (antecedent features that distinguish cases from controls) primarily have been FSSs. Indeed, the odds of IC/BPS increase with the number of such syndromes present. Surgery was long thought to be a risk factor for IC/BPS, but analyses adjusting for FSSs refuted that association. About one-third of patients appear to have bacterial cystitis at the onset of IC/BPS.

The natural history of IC/BPS is not known. Although studies from urology and urogynecology practices have been interpreted as showing that IC/BPS lasts for the lifetime of the patient, population studies suggest that some individuals with IC/BPS do not consult specialists and may not seek medical care at all, and most prevalence studies do not show an upward trend with age—a pattern that would be expected with incident cases throughout adulthood followed by lifetime persistence of a nonfatal disease. It may be reasonable to conclude that patients in a urology practice represent those with the most severe and recalcitrant IC/BPS.

PATHOLOGY

For the $\leq 10\%$ of IC/BPS patients who have a Hunner's lesion, the term *interstitial cystitis* may indeed describe the histopathologic picture. Most of these patients have substantive inflammation, mast cells, and granulation tissue. However, in the 90% of patients without such lesions, the bladder mucosa and interstitium are relatively normal, with scant inflammation.

ETIOLOGY

Numerous hypotheses about the pathogenesis of IC/BPS have been put forward. It is not surprising that most early theories focused on the bladder. For instance, IC/BPS has been investigated as a chronic bladder infection. Sophisticated technologies have not identified a causative organism in urine or in bladder tissue; however, the patients studied by these methods had IC/BPS of long duration, and the results do not preclude the possibility that infection may trigger the syndrome or may be a feature of early IC/BPS. Other inflammatory factors, including a role for mast cells, have been postulated, but (as noted above) the 90% of patients without a Hunner's ulcer have little bladder inflammation and do not have a prominence of mast cells in bladder tissue. Autoimmunity has been considered, but autoantibodies are low in titer, nonspecific, and thought to be a result rather than a cause of IC/BPS. Increased permeability of the bladder mucosa due to defective epithelium or glycosaminoglycan (the bladder's mucous coating) has been studied frequently, but the findings have been inconclusive.

Investigations of causes outside the bladder have been prompted by the presence of comorbid FSSs. Many patients with FSSs have abnormal pain sensitivity as evidenced by (1) low pain thresholds in body areas unrelated to the diagnosed syndrome, (2) dysfunctional descending neurologic control of tactile signals, and (3) enhanced brain responses to touch in functional neuroimaging studies. Moreover, in patients with IC/BPS, body surfaces remote from the bladder are more sensitive to pain than is the case in individuals without IC/BPS. All

these findings are consistent with upregulation of sensory processing in the brain. Indeed, a prevailing theory is that these concomitantly occurring syndromes have in common an abnormality of brain processing of sensory input. However, antecedence is a critical criterion for causality, and no study has demonstrated that abnormal pain sensitivity precedes either IC/BPS or the FSSs.

CLINICAL PRESENTATION

In some patients, IC/BPS has a gradual onset, and/or the cardinal symptoms of pain, urgency, frequency, and nocturia appear sequentially in no consistent order. Other patients can identify the exact date of onset of IC/BPS symptoms. More than half of the latter patients describe dysuria beginning on that date. As stated, only a minority of IC/BPS patients who obtain medical care soon after symptom onset have uropathogenic bacteria or leukocytes in the urine. These patients—and many others with new-onset IC/BPS—are treated with antibiotics for presumptive bacterial cystitis or, if male, chronic bacterial prostatitis. Persistent or recurring symptoms without bacteriuria eventually prompt a differential diagnosis, and IC/BPS is considered. Traditionally, the diagnosis of IC/BPS has been delayed for years, but recent interest in the disease has shortened this interval.

The pain of IC/BPS includes suprapubic prominence and changes with the voiding cycle. Two-thirds of women with IC/BPS report two or more sites of pain. The most common site (involved in 80% of women) and generally the one with the most severe pain is the suprapubic area. About 35% of female patients have pain in the urethra, 25% in other parts of the vulva, and 30% in nonurogenital areas, mostly the low back and also the anterior or posterior thighs or the buttocks. The pain of IC/BPS is most commonly described as aching, pressing, throbbing, tender, and/or piercing. What may distinguish IC/BPS from other pelvic pain is that, in 95% of patients, bladder filling exacerbates the pain and/or bladder emptying relieves it. Almost as many patients report a puzzling pattern in which certain dietary substances worsen the pain of IC/BPS. Smaller proportions—but still the majority—of patients report that their IC/BPS pain is worsened by menstruation, stress, tight clothing, exercise, and riding in a car as well as during or after vaginal intercourse.

The urethral and vulvar pains of IC/BPS merit special mention. In addition to the descriptive adjectives for IC/BPS mentioned above, these pains commonly are described as burning, stinging, and sharp and as being worsened by touch, tampons, and vaginal intercourse. Patients report that urethral pain increases during urination and generally lessens afterward. These characteristics have commonly resulted in diagnosis of the urethral pain of IC/BPS as chronic urethral syndrome and the vulvar pain as vulvodynia.

In many patients with IC/BPS, there is a link between pain and urinary urgency; that is, two-thirds of patients describe the urge to urinate as a desire to relieve their bladder pain. Only 20% report that the urge stems from a desire to prevent incontinence; indeed, very few patients with IC/BPS are incontinent. As mentioned above, urinary frequency can be severe, with $\sim 85\%$ of patients voiding more than 10 times per 24 h and some as often as 60 times. Voiding continues through the night, and nocturia is common, frequent, and often associated with sleep deprivation.

Beyond these common symptoms of IC/BPS, additional urinary and other symptoms may be present. Among the urinary symptoms are difficulty in starting urine flow, perceptions of difficulty in emptying the bladder, and bladder spasms. Other symptoms include the manifestations of comorbid FSSs as well as symptoms that do not constitute recognized syndromes, such as numbness, muscle spasms, dizziness, ringing in the ears, and blurred vision.

The pain, urgency, and frequency of IC/BPS can be debilitating. Proximity to a bathroom is a continual focus, and patients report difficulties in the workplace, leisure activities, travel, and simply leaving home. Familial and sexual relationships can be strained.

DIAGNOSIS

Traditionally, IC/BPS has been considered a rare condition that is diagnosed by urologists at cystoscopy. However, this disorder is much