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CURRENT OPINION

The Challenges of Interstitial Cystitis: Current Status and Future Prospects

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Abstract Interstitial cystitis/bladder pain syndrome (IC/BPS) is a syndrome of unpleasant bladder sensations and lower urinary tract symptoms. The three main proposed etiologies are bladder urothelial dysfunction, bladder inflammation (possible neurogenic), and neuropathic pain. Despite decades of basic and clinical research, IC/BPS remains difficult to treat. A variety of treatments are used, each aimed towards one etiology. For example, glycosaminoglycans are thought to improve the urothelial permeability barrier, anti-inflammatory agents are used to decrease general inflammation, and mast cell stabilizers and/or antagonists of mast cell products are used in the treatment of neurogenic inflammation. In the (unfortunately frequent) event that a treatment fails, possible reasons are that (1) the clinician is aiming towards the wrong etiology for that patient (i.e., the treatment is off target) or (2) the correct etiology is being targeted, but the treatment is not ameliorating it (i.e., the treatment is sub-therapeutic). This is a crucial distinction, because an off-target treatment should be abandoned, but a sub-therapeutic treatment should be escalated. Currently, our inability to make this crucial distinction is the greatest obstacle to effective treatment. An important future advance would be to identify urine or serum biomarkers specific to each etiologic target. Then, each biomarker could be used to select appropriate patients for each treatment and monitor the treatment's effect on its intended target.

Key Points

Interstitial cystitis/bladder pain syndrome has multiple proposed etiologies, each of which serves as a theoretical rationale for one or more treatment options.

A clinically feasible diagnostic biomarker has yet to be developed, and it may not be possible for one biomarker to diagnose accurately a multifactorial syndrome.

We summarize the proposed etiologies with their relevant treatments and biomarkers. Key roles for biomarkers will be to help select a treatment that is on-target for a given patient's pathophysiology, and to monitor whether that treatment is having the desired effect on the underlying pathophysiology.

1 Introduction

The cardinal symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS) include unpleasant bladder sensations (e.g., pain, pressure) and lower urinary tract symptoms in the absence of infection or other identifiable pathology. In general, the etiologies fall into three broad categories that may be inter-related: (1) bladder epithelial dysfunction, which may lead to increased permeability and/or increased

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sensitivity, possibly via autocrine secretion of neurochemicals that effect bladder afferent function; (2) bladder inflammation; or (3) neuropathic pain, i.e., pain related to dysfunction of one or more nerves, including peripheral, central, and/or failure of endogenous inhibitory pathways. Finally, although standard urine cultures are negative in IC/BPS, various fastidious organisms have been investigated as potential infection sources.

1.1 Challenges of the Existing Diagnosis and Treatment Guidelines

At this time, the major guidelines include those from the European Society for the Study of IC (ESSIC), the Society of Interstitial Cystitis of Japan (SICJ), and the American Urological Association (AUA) [1–3].

All guidelines recommend history, exam, urinalysis, and urine culture for diagnosis. However, from there, the guidelines differ regarding the need for additional tests to rule out confusable diseases (e.g., specialized urine cultures) or to formalize the designation of IC/BPS (e.g., cystoscopy with bladder distention).

Two guidelines (SICJ and AUA) also discuss treatment. The challenge here is that the guidelines do little more than list the treatment options. Except for the AUA guideline advice to progress through tiers based on levels of risk, and to stop ineffective treatment after a clinically meaningful interval, there is little direction for the clinician to choose or change a treatment regimen (this is not the fault of the guideline committees, but simply reflects a lack of evidence in this area).

There are multiple reasons for bladder pain. To be effective, a treatment must address a given patient's pathophysiology. If a treatment fails, possible reasons are that (1) the clinician is aiming towards the wrong pathophysiology for that patient (i.e., the treatment is off target) or (2) the correct pathophysiology is being targeted, but the treatment is not ameliorating it (i.e., the treatment is subtherapeutic). In addition, without knowing any given patient's pathophysiology, it is difficult to develop new therapies and even more difficult to test them in randomized trials. If the trial enrolls patients for whom the treatment is off target, then the overall failure rate may be high enough to mask the benefit obtained by the relevant patients.

1.2 Overview of Biomarkers

Biomarkers are generally considered as tools for diagnosing a given disease and/or evaluating its severity (e.g., for diabetes mellitus, hemoglobin A_{1c} serves both purposes). For IC/BPS, investigators have tested numerous urine and serum components. While many differed between IC/BPS patients and healthy controls, most had too much overlap between IC/BPS and control values to be reliable diagnostic markers. One exception is urine anti-proliferative factor (APF), which was found in almost all IC/BPS patients but in very few controls or patients with confusable diseases [4]. Parsons et al. [5] described another possible exception: a urine cationic fraction. They found that cultured urothelial cells had decreased proliferation if exposed to cationic fractions from IC versus control urine, with minimal overlap in the proliferation assay signal between the two groups [5]. Unfortunately, this and the urine APF assay methods are too cumbersome for routine clinical use. The only reported serum marker unique to IC/BPS is an infrared microspectroscopy signature, which remains under investigation [6].

Rather than looking for a 'yes or no' diagnosis, another use for biomarkers would be to help clinicians select on-target treatments, and assess whether those treatments are therapeutic. The sections below discuss individual biomarkers in the context of the relevant etiologies and targeted treatments.

2 Bladder Epithelial Dysfunction

2.1 Bladder Urothelial Permeability

A longstanding theory is that the urothelium in IC/BPS is too permeable, allowing potassium and other noxious urine components to cross the barrier. Glycosaminoglycans (GAGs) are thought to improve this problem and are used as treatments. GAG treatments include oral pentosanpolysulfate (PPS) and intravesical heparin, PPS, chondroitin sulfate, or hyaluronic acid. Unfortunately, not all patients respond to GAG therapy. Multiple studies testing oral PPS versus placebo showed variable results [7, 8]. Intravesical heparin, usually combined with local anesthetics and other ingredients, has reported success rates from 56 to 77 % [1, 9]. Hyaluronic acid and chondroitin sulfate helped some patients in uncontrolled trials, but did not outperform placebo in randomized trials [10–12].

Intravesical liposomes have been investigated as another method for improving the bladder permeability barrier. They can be used alone or encapsulated with other therapeutic agents. In a prospective trial of four weekly treatments with empty liposomes versus 4 weeks of oral PPS (100 mg three times daily), both groups had similar levels of symptom improvement [13]. A recent pilot study used PPS 400 mg encapsulated into liposomes for eight patients for whom prior oral and/or intravesical PPS had failed [14]. After 3 months of instillation every other week, mean IC symptom index/IC problem index (ICSI/ICPI) score decreased from 26.5 to 13.8 and mean pain/urgency/frequency (PUF) score decreased from 24.9 to 12.1 [14].

While some patients achieve excellent symptom improvement with the above therapies, other patients are refractory. For the refractory patients, a valid biomarker could help the clinician decide whether the treatment is off target (and should be abandoned) or sub-therapeutic (and should be escalated with higher doses and/or more frequent administration). Also, as eloquently stated by Nickel et al. [12], a reliable biomarker could help select the correct patients in the first place. Unfortunately, no such biomarkers are currently available. Urine levels of several GAGs have been reported differ between IC/BPS patients and controls [15], and the urine cationic fraction from IC/BPS patients was cytotoxic [5]. However, these potential markers have not been investigated as tools for selecting patients for whom GAG therapy is on target.

Parsons et al. [16] proposed the potassium sensitivity test (PST) as a method for identifying IC/BPS patients with increased urothelial permeability. For oral PPS, the test turned out not to predict response rate (approximately 60 % for both PST-positive and PST-negative patients) [16]. For intravesical hyaluronic acid, one trial used a modified PST (potassium chloride 0.3 M instead of 0.4 M) and found at least a moderate response for 52 % of PST-positive patients but only 23 % of PST-negative patients [17].

2.2 Altered Urothelial Sensitivity

In addition to serving as a permeability barrier, the urothelium is also involved in sensory function and cell signaling [18]. Abnormalities in these functions may have a role in IC/BPS. For example, urothelial cells from IC/BPS patients have increased expression of purinergic receptor protein and increased release of adenosine triphosphate (ATP) [18]. This line of research is fairly new, and biomarkers for these abnormalities have not been established for use in patient phenotyping or treatment selection.

3 Inflammation

3.1 Generalized Inflammation

Patients with Hunner lesions exemplify effective phenotype-directed treatment. When these lesions are identified, the AUA guideline recommends cystoscopic treatment: fulguration or injection of triamcinolone. This usually provides marked symptom relief. If the lesions recur rapidly or are too extensive for complete fulguration, then anti-inflammatory treatments are often effective. For example, cyclosporine A is a fifth-tier option in the AUA guideline and is effective for most patients with Hunner lesions, although some patients must stop due to side effects [19]. Oral corticosteroids have been reported to improve symptoms in about 50 % of patients with Hunner lesions [20, 21], but these treatments are not recommended by the AUA guideline as they can cause significant side effects [1]. Nonsteroidal anti-inflammatory drugs decrease inflammation, but there are theoretical reasons to avoid them in IC/BPS: they have been shown to adversely affect the bladder urothelium in animal studies, can trigger mast cell secretion in high doses, and can induce IC/BPS in humans [22–24].

While Hunner lesions invariably signify bladder inflammation, the converse is not necessarily true. Patients can have inflammation on bladder biopsy, even without visible Hunner lesions. For example, in a study of 50 Belgian patients using the ESSIC classification, 12 patients were classified as 1C and 33 were 2C (1 = normal cystoscopy, 2 = glomerulations, 3 = Hunner lesions, and C = biopsy findings of inflammation, mastocytosis, granulation tissue or fibrosis) [25]. In another European cohort, in 13 IC/BPS patients, three were ESSIC 3C and eight were 2C [26]. In a US cohort of 63 patients without Hunner lesions, 17 had severe inflammation on bladder biopsy [27].

Because some patients have bladder inflammation even without Hunner lesions, they may be appropriate for anti-inflammatory therapy. The problem is how to select them, especially considering the narrow therapeutic index of immunosuppressive treatments. For now, bladder biopsy is the most reliable method, but it is invasive and expensive. Ideally, urine biomarkers could substitute for biopsy in identifying patients with bladder inflammation. Numerous inflammatory markers have been found to differ between IC/BPS and control urine [15, 28], but very little research has compared urine biomarkers with the relevant biopsy features. Furthermore, these markers have not been investigated as markers to select patients for whom anti-inflammatory treatment would be on target.

It may be possible to decrease bladder inflammation without global immunosuppression. For example, intravesical dimethylsulfoxide (DMSO) has anti-inflammatory properties, is approved for IC and is a second-tier option in the AUA guideline. The original studies did not specifically select for bladder inflammation, and in clinical practice it is used for patients with and without Hunner lesions. As monotherapy, DMSO had a wide range of efficacy both in randomized trials (47–93 %) and in observational studies (25–90 %) [1]. It is also used as part of a cocktail, usually with some combination of heparin, sodium bicarbonate, local anesthetic, and/or corticosteroid [1]. One would expect corticosteroids to increase efficacy, but the optimal additives have not been determined. For that matter, 50 ml of 50 % DMSO may not be optimal. DMSO in high concentrations stimulates mast cells, which may explain the increased symptoms experienced by some patients [24].

Lower concentrations (≤10 %) inhibit mast cell secretion [24] and may deserve further research, especially for patients for whom anti-mast cell treatment would be on target.

Although bladder instillations are less risky than systemic immune suppression, they do involve expense, discomfort, and the risk of infection. Therefore, ideal patient management still requires biomarkers to select patients for whom the instillations are on target and to detect when they are sub-therapeutic.

3.2 Neurogenic Inflammation

Neurogenic inflammation occurs when afferent neurons release inflammatory mediators, leading to a self-perpetuating cycle in which activated inflammatory cells (e.g., mast cells, leukocytes) stimulate and sensitize the neurons, which then release more inflammatory mediators, etc. [29].

Based on biopsy findings of bladder mast cells in IC/BPS, and on mast cells being observed close to nerve endings, IC/BPS has been proposed to be a type of neurogenic inflammation. Because mast cells are thought to be involved in the self-perpetuating cycle, various mast cell-directed treatments have been investigated. These include cromolyn (mast cell stabilizer), hydroxyzine (histamine 1 receptor antagonist and possible mast cell stabilizer), cimetidine (histamine 2 receptor antagonist), and quercetin (inhibitor of mast cell proliferation and activation) [30–33]. Of these, only cimetidine has demonstrated benefit in a controlled trial, and this trial specifically enrolled patients who had inflammation on bladder biopsies [30]. Of note, PPS has mast cell-stabilizing properties, and this may contribute to its benefit for IC/BPS patients [31].

While some patients respond well, these agents generally have low success rates. This raises the same question as discussed for the other IC/BPS pathophysiologies: were the therapies off target or sub-therapeutic? Ideally, urine markers of mast cell activation could help. Several mast cell mediators have been shown to be elevated for IC/BPS patients compared with controls: histamine, methylhistamine, 1-4 methylimidazole acetic acid, mast cell tryptase, eosinophil cationic protein, and leukotriene E4 [15]. However, none of these have been investigated as a marker to predict or follow response to mast cell-directed treatment. This remains another important area for future research.

3.3 Inflammation and Bladder Hydrodistention

Bladder hydrodistention is a third-tier treatment option in the AUA guideline. Transient improvement occurs in 15–60 % of patients [34, 35]. The mechanism of benefit is unknown. Cole et al. [35] found that patient symptoms and cystoscopic findings did not associate with post-distention symptom improvement. On the other hand, bladder biopsy findings of severe inflammation [36] and high mast cell counts [37] were associated with symptom improvement. A possible mechanism is that distention may cause widespread degranulation of bladder mast cells, after which symptoms would improve until the mast cell population regenerated. Consistent with this hypothesis, Yun et al. [38] found increased urine histamine levels (indicating mast cell degranulation) after hydrodistention.

Evaluating for other possible mechanisms, Erickson et al. [39] compared pre and post-distention levels for several urine markers: APF, epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), cyclic guanosine monophosphate, and interleukins 6 and 8. After distention, the interleukins did not change, but APF and HB-EGF changed towards normal (decreased and increased, respectively). Thus, another possible mechanism is that distention increased autocrine secretion of HB-EGF, which can ameliorate the effects of APF and may have improved urothelial function.

Hydrodistention may also improve IC/BPS symptoms by other effects, e.g., mechanical stretch or pressure may alter afferent nerve terminals in the bladder.

4 Neuropathic Pain

4.1 Neuropathic Pain in Interstitial Cystitis/Bladder Pain Syndrome

At its most basic definition, neuropathic pain is due to one or more abnormalities in the nervous system. Abnormalities reported in IC/BPS patients include increased number of afferent peripheral nerves [40], alterations in brain structure and function [41, 42], and failure of endogenous inhibitory pathways [43]. In theory, IC/BPS could also involve increased sensitivity of afferent peripheral nerves and/or hyperalgesia at the spinal cord level, but these have not been specifically demonstrated in human IC/BPS patients.

For neuropathic pain in general, first-line treatments are tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors [44]. Among these, amitriptyline is the most commonly used for IC/BPS. In two randomized trials, only one showed amitriptyline to outperform placebo [45, 46]. However, these two trials had an important difference in study design. The second trial provided education and diet advice to all patients, leading to a significant symptom improvement in the 'placebo' arm. These results should not be construed as evidence against amitriptyline, but rather as evidence in favor of education.

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was effective for diabetic neuropathy but has not been well established for other types of neuropathic pain. For IC/BPS, a single-arm cohort trial showed no benefit [47]. Selective serotonin reuptake inhibitors have not been studied in IC/BPS, but, for neuropathic pain in general, the guidelines either do not mention them, or mention them as less effective options [48].

Botulinum toxin is well known as a muscle paralytic because it inhibits release of acetylcholine from nerve endings. However, it also inhibits release of other neurotransmitters relevant to sensation [49] and improved IC/BPS symptoms in single-arm trials [1]. Two randomized trials compared bladder hydrodistention with versus without prior [50] or concurrent [34] botulinum toxin injections. Both trials showed higher success rates for hydrodistention + botulinum toxin than for hydrodistention alone.

Like the other treatments described throughout this article, these treatments for neuropathic pain are not uniformly effective. Again, for the failures, we do not know whether the agent was off target or sub-therapeutic. A biomarker for neuropathic pain would help to make progress for these patients.

4.2 Nerve Growth Factor as a Biomarker

Nerve growth factor (NGF) is produced by many types of tissue, including urothelium and smooth muscle [51]. It is essential for the development of sensory and sympathetic neurons [52], but also increases pain by affecting nociceptive neurons and by stimulating mast cells to release histamine and other mediators [52].

Three studies have evaluated NGF in bladder biopsies. The first showed lower NGF protein levels for patients with stress incontinence than for those with idiopathic sensory urgency, chronic cystitis, or IC [53]. The second showed increased NGF messenger RNA (mRNA) levels for IC/BPS patients versus controls, as well as differences in tissue localization: the patients had NGF in the urothelium and suburothelium, while controls had NGF only in the apical urothelium [54]. The third study showed higher NGF protein levels for IC/BPS patients than for controls, and bladder NGF levels were associated with severity of inflammation [55].

Urine NGF has been proposed as a biomarker for IC/BPS [56] but is not specific for this disorder. Increased urine NGF levels have also been reported for neurogenic bladder, idiopathic overactive bladder, urinary tract infection, bladder tumors, and renal calculi [57, 58]. Another concern is that most prior studies of urine NGF used the Emax® Immunoassay from Promega, which may not be accurate in urine due to cross-reaction with immunoglobulin G [59]. As this assay is no longer available, it may be difficult to reconcile the early literature with future studies that use different assays.

5 Infection

Many investigators have sought fastidious organisms in the urine or bladder tissue of IC/BPS patients [60], but have not provided strong evidence that viruses or other organisms cause IC/BPS.

The most recent infectious hypothesis concerns BK virus. A 2014 study found positive urine BK virus titers in 11 of 15 IC/BPS patients but not in controls [26]. A total of 13 patients had cystoscopy and biopsy. All biopsies showed inflammation, regardless of virus titer. Cystoscopy showed glomerulations or Hunner lesions for nine of nine titer-positive patients but only one of four titer-negative patients. Two patients with high titers received intravenous cidofovir, but subsequently failed and underwent cystectomy.

A 2015 study enrolled 50 IC/BPS patients for whom noninvasive treatment had failed and underwent cystoscopy with distention [61]. Of 49 evaluable patients, 27 had Hunner lesions and 22 had glomerulations. Rates of positive BK virus titers were 67 % and 23 %, respectively (approximately 32 % of controls were positive, similar to levels in the general population).

The clinical implications are unclear because BK virus is found in the general population [61] and because almost no patients received antiviral treatment.

6 Future Prospects

As IC/BPS can result from several different underlying pathologies, it seems unlikely that we will find single treatment to cure all cases. Future advances will be made by developing new therapeutic techniques, such as inserting genes for desired products (e.g., endogenous opioids, interleukin-4, or tumor necrosis factor soluble receptors) directly into the urothelium [62], and by developing accurate biomarkers to correctly pair treatments with underlying pathologies and track patient response.

Compliance with Ethical Standards

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