OPINION ARTICLE

Interstitial cystitis/bladder pain syndrome research: the answer may be just around the corner [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract
Despite tremendous efforts, a large cadre of excellent researchers have been unable to definitively identify any cause of interstitial cystitis/bladder pain syndrome (IC/BPS) or develop more effective treatments. Newer research suggests that IC/BPS may have an infectious etiology. IC/BPS may also be related to mast cells, which have not been re-evaluated adequately. Many of the new investigative techniques, such as DNA/genomic analysis, microbiomes, and mycobiomes, applied from the fields of microbiology, infectious diseases, gastroenterology and mast cell specialists, have not have been fully utilized and applied to the field of urology and the study IC/BPS. Additional collaboration with these other fields of medicine may have a substantial impact on IC/BPS research and will likely move the urology community much closer to the causes of, and possible cures for, this most debilitating disease.

Keywords
Interstitial Cystitis/Bladder Pain Syndrome IC/BPS, Bladder Pain Syndrome (BPS), Interstitial Cystitis (IC), IC/BPS Research, IC/BPS and biofilms, IC/BPS and mast cells

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Introduction

The first article on interstitial cystitis (IC) was published in the United States in 1887. However, research in earnest in the U.S. did not begin until the first National Institutes of Health (NIH) meeting held one hundred years later, in 1987. Although much progress has been made since that time, the cause and cure of interstitial cystitis/bladder pain syndrome (IC/BPS) remain elusive.

IC affects up to 10 million people in the U.S.

The next step could be to create specific phages (lytic viruses) that could penetrate the biofilms of specific organisms that might be found on these urothelial cells, followed by administration of appropriate antibiotics. This might be one way to cure IC/BPS if extracellular organisms are the cause.

Mast cells and mast cell activation disease

Mast cells reside in all vascularized tissues of the body, including the bladder. They are generally found in close proximity to blood vessels and nerves. Mast cells contain over 200 types of granules/mediators. The hypothesis that inappropriate chronic mast cell activation may be an integral element, and perhaps even the root cause of IC/BPS in at least some patients, should be considered and revisited employing updated techniques.

The mast cell biopsy should be re-evaluated in the field of IC/BPS using the stain most specific for mast cells, CD117. In addition, an accurate measurement of the levels of these mast cell granules (e.g. tryptase, histamine, N-methylhistamine, heparin and prostaglandin D2, among others) many of which have quite short half-lives and great thermalobility) in urine samples has been quite challenging to determine and should be re-assessed.

This hinders or even renders impossible, the ability to demonstrate in the IC/BPS population that mast cell activation exists. Laboratory techniques have improved with time and assessment of IC/BPS patients for biochemical evidence of mast cell activation is becoming more feasible, especially using CD117 staining. Although a paper published in 2015 addressed a great deal of research on mast cells and mast cell activation syndrome (MCAS), it was not specific for IC/BPS.

If mast cell mediators can be consistently found in the urine of IC/BPS patients, then inappropriate mast cell content release might explain the etiology of IC/BPS patients, or at least one etiology of IC/BPS. This might provide additional means for diagnostic testing and/or be a marker for the condition. It may also point towards more effective treatment directed at specific inflammatory mast cell mediators, reduce time to diagnosis, and provide the basis for at least one component of a classification system for the disease.

Simply relying on the number of mast cells seen on biopsy is not enough. The number of mast cells may not be as important as their level of activation and/or degranulation. Mast cells may be hyper-responsive and degranulate more frequently in IC/BPS if extracellular organisms are the cause.

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This hinders or even renders impossible, the ability to demonstrate in the IC/BPS population that mast cell activation exists. Laboratory techniques have improved with time and assessment of IC/BPS patients for biochemical evidence of mast cell activation is becoming more feasible, especially using CD117 staining. Although a paper published in 2015 addressed a great deal of research on mast cells and mast cell activation syndrome (MCAS), it was not specific for IC/BPS.

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Simply relying on the number of mast cells seen on biopsy is not enough. The number of mast cells may not be as important as their level of activation and/or degranulation. Mast cells may be hyper-responsive and degranulate more frequently in response to variable trigger stimuli or may selectively release specific inflammatory mediators in response to a certain type of stimulus. The release of inflammatory mediators without degranulation of the mast cell may also occur. Proper histochemical and/or immunohistochemical staining of biopsied

Future directions in research

Extracellular and intracellular organisms

There are many similarities between the lining of the genitourinary tract and gastrointestinal tract. Pathologic extracellular organisms have been identified on the cells lining the gastrointestinal tract, but have yet to be found on the urothelial lining of the bladder. A search for other pathologic extracellular organisms on IC/BPS urothelium using modern investigative techniques may prove enlightening. It may hold the key to identifying at least some etiologies of IC/BPS and could lead to treatments that may dramatically reduce symptoms or possibly lead to a cure.

Familial Crohn’s Disease is a small subset of Crohn’s Disease. Although admittedly a small sample size was used, in 2017, researchers reported the presence of three organisms (Candida tropicalis, Escherichia coli, and Serratia marcescens) on the lining of the gastrointestinal tract, detected using DNA sequencing. Many organisms stick to the lining of the intestines via fimbiae and produce biofilms to protect themselves; thus, allowing these organisms to escape the body’s normal protective immune responses and form an impenetrable barrier to antibiotics. Recently (April 2019), it was shown that the above three organisms were found in elevated amounts in a cohort of patients with Crohn’s Disease and that the use of specific probiotics significantly decreased the number of these pathologic organisms; thereby reducing the amount of inflammation that they caused.

In additional to taking a bladder biopsy, urologic researchers could further investigate IC/BPS patients whose urine cultures are negative, despite the patients being clinically symptomatic. PCR is one such technique. Another would be to take a second sample from these patients, spin down the urine samples, pour off the supernatant, and look at the remaining urothelial cells using a confocal scanning laser microscope to determine whether there are any bacteria or fungi attached to the cells (personal communication with Dr. Mamoud Ghanem, Case Western Reserve University). If this technique reveals that specific organisms are present on a large number of IC/BPS urothelial cells, and not in controls, larger studies should be reproduced at other medical centers in order to validate this technique. If positive, this may indicate that IC/BPS has an infectious etiology, despite negative urine cultures.

The number of mast cells may not be as important as their level of activation and/or degranulation. Mast cells may be hyper-responsive and degranulate more frequently in response to variable trigger stimuli or may selectively release specific inflammatory mediators in response to a certain type of stimulus. The release of inflammatory mediators without degranulation of the mast cell may also occur. Proper histochemical and/or immunohistochemical staining of biopsied

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tissue is critical for revealing the mast cells therein, as these cells usually cannot be recognized as mast cells with routine hematoxylin and eosin staining, instead being mistaken for other types of cells such as lymphocytes or macrophages. The best staining for mast cells is CD117 immunohistochemical staining, which is independent of the mast cell’s state of activation and is seen brightly on mast cells (a pattern seen on virtually no other cells). Certain other histochemical stains, such as tryptase and toluidine blue, have long been used by pathologists to identify mast cells. However, these stains principally target the mast cells’ granules; thus, they may not be as revealing for MCAS as CD117 can be, given that MCAS is a disease whose dominant feature is inappropriate mast cell activation and whose cellular-level pathology is dominated by mast cell degranulation, including complete degranulation which leaves an ‘empty’ cell that can be identified\(^{[10-13]}\).

Mast cells and transgranulation

In addition to degranulation, mast cell contents are able to transgranulate to nerves via the formation of filopodia (thin, finger-like projections) that attach directly to the neuronal membranes of nerves, including nerves within the bladder. The contents of the mast cells empty directly into the nerve cells via endocytosis. Transgranulation of mast cell contents to nerves in the brain was shown via time-lapse photography using an electron microscope in 2005\(^{[14]}\). It is possible that sensory nerves in the bladder are triggered by mediators released from mast cells (either in the bladder, elsewhere or both), generating impulses that travel to the spinal cord and, from there, to the pain centers in the brain. This may be an explanation for the pelvic pain symptoms seen in many patients with IC/BPS.

Conclusion

Moving forward, it is critical that researchers in urology think ‘outside the box’ and increase their collaboration with researchers in other fields of medicine that may relate to IC/BPS, such as gastroenterology, microbiology, Infectious disease, and mast cell specialists. Possibilities discussed in detail in this paper include extracellular organisms that may form biofilms on the surface of the urothelium of the bladder lining (using Crohn’s Disease as a model). This can result in a negative urine culture, yet the painful bladder symptoms might still be caused by an infectious agent. Mast cells may play a much larger role in IC/BPS than previously thought. Hopefully, in the future, National Institutes of Diabetes, Digestive and Kidney (NIDDK) grants will make infection and mast cell involvement in IC/BPS a high priority in their research portfolio.

It is important to keep in mind how far we have to go, how much misery this condition is still causing, and how many hundreds of thousands of lives IC/BPS continues to ravage. The pain can be so intolerable that some patients have been driven to take their own lives\(^{[15]}\). Additional research on areas discussed in this paper should be undertaken and other areas re-evaluated. Since 1987, when the first NIDDK conference on IC was held, over 30 years have come and gone. The need for adequate treatments and a cure are urgent, yet little practical help for patients has been found\(^{[16]}\).

Data availability

No data is associated with this article.

Grant information

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This publication is not a report on the results of a clinical or a basic scientific study. Its an opinion article by the category. We do not have to expect proof of hypotheses, new findings, or innovation. However, we get the logically well-founded opinion of an author, who has been deeply involved in the topic of interstitial cystitis for more than three decades. She points out two challenging, yet not wholly cleared fields of the etiopathogenesis of IC/BPS: namely the role of mastocytosis and the possible presence of unidentified “bacteria or fungi attached to the cells”.

Much research was performed worldwide, and many publications are available regarding these two suggested topics, but no conclusion could be drawn. This and the newly available sophisticated lab techniques make still sense to revive these research works.

Yet I think, there are a series of other (maybe even more compelling) research topics: to define the role of microbiome in IC/BPS, to develop more objective and non-invasive diagnostic tools, to find the most efficacious composition of the bladder cocktails, to reduce the costs and invasiveness of the IC/BPS therapy, to work out a unified long-term follow-up system of the patients' condition, etc.

I agree entirely with the author on the importance of future cooperation with other specialities of medicine like "gastroenterology, microbiology, infectious disease, and mast cell specialists" as it is mentioned, but also with gynaecologists, pharmacologists, dietetics, physiotherapists, psychologists, etc. There is an evident need for fruitful interactive teamwork, yet it is doubtless for the majority of researchers dealing with IC/BPS, that a well-functioning, complete team is nowadays rather a dream than reality.

Everybody knows that certain negative tendencies are setting back the optimal flow of the desired research work. Basic research is less attractive for the younger generation of urologists than laparoscopy, robotics, radical tumour-surgery, infectiology, etc.

In summary, I can state that the thoughts of the author are worth to be considered. She does not want to
propose a complete program for IC/BPS research, but even in this limited extent, her opinion article is enormously essential to raise the awareness and to direct the attention of the society to this disease. Therefore, I definitely support this article to be indexed.

Is the topic of the opinion article discussed accurately in the context of the current literature? Yes

Are all factual statements correct and adequately supported by citations? Partly

Are arguments sufficiently supported by evidence from the published literature? Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments? Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Treatment of IC/BPS, especially developing new way of local drug delivery and less expensive treatment modalities.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Christopher K. Payne
Department of Urology, Stanford University Medical School, Stanford, CA, USA

This is a hopeful article, pointing out the many exciting areas where scientific advances might be applied to better understand and treat patients with chronic bladder pain. Unfortunately, while the individual statements are factually correct, the guiding vision is rooted in the same narrow conception of disease that has produced so many failed studies over the past decades. The author acknowledges that IC/BPS is not well understood, "It is unclear if IC/BPS is one disease, one disease associated with other conditions, such as chronic fatigue syndrome, Crohn’s disease, irritable bowel syndrome, endometriosis and vulvodynia, for example, or a systemic condition with a urinary or hematologic marker yet to be found."

In 1978, Meares and Stamey hypothesized that "petechia-like hemorrhages (glomerulations) on the second distention of the bladder is the hallmark of interstitial cystitis, and that a reduced bladder capacity and a Hunner’s ulcer represent a different (classic stage of the disease).” From this point glomerulations became the key to diagnosis (even worse, now we rely only on symptoms to diagnose BPS). However,
this hypothesis was wrong. After over 40 years there is not even a single case report of a patient progressing from glomerulations to classic IC. A recent review concluded that there was, "no convincing evidence . . . that glomerulation should be included in the diagnosis or phenotyping of BPS/IC. 2"

In fact, classic ulcerative Interstitial Cystitis (IC) is almost certainly a unique disease and, if thought leaders were to acknowledge it as such, great progress might be made in this area. The author's approaches might even pay off in this population.

On the other hand, Bladder Pain Syndrome (BPS) is no more than what its name implies—a syndrome, a group of patients with similar symptoms. This may be useful for epidemiological purposes, but it is of little value clinically. These patients have many different individual causes for their symptoms. It is usually possible to identify the primary symptom drivers in individual patients and, using this, treat them successfully. Individual patients can achieve remission with therapies as diverse as bladder instillations, myofascial physical therapy, and treatment aimed at central sensitization. It does not make sense to enrol such diverse BPS patients in clinical or research trials; in particular, there is no rationale to combine IC and BPS in any type of research protocol.

I agree with the author that, "researchers in urology think 'outside the box' and increase their collaboration with researchers in other fields of medicine". However, studies should be done with reasonably homogeneous groups of patients and using appropriate hypotheses. It may well be worth revisiting mast cell abnormalities in cohorts of patients with multiple allergies. Advances in infectious disease might plausibly be applied to those classic IC or a clear bladder-centric phenotype. A great many patients have risk factors for and evidence of central sensitization. The NIDDK MAPP study group is exploring such patients and has already made many relevant observations. As the author emphasizes, "It is important to keep in mind how far we have to go, how much misery this condition is still causing, and how many hundreds of thousands of lives IC/BPS continues to ravage." Nevertheless, research funding and effort is a scarce commodity and must be directed wisely. Continuing to use the same paradigm that has produced so little will not be wise.

References

Is the topic of the opinion article discussed accurately in the context of the current literature?
Partly

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
No

Competing Interests: Consultant/Medical Advisory Board: Astellas Pharma, Inc.
**Reviewer Expertise:** I am fellowship trained in Female Urology and Pelvic Reconstructive Surgery. I was the Director of Female Urology at Stanford for over 20 years. I am now in a private practice focused on Urologic Chronic Pelvic Pain.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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