

AUA Meeting Brings Big IC News, New Treatment Ideas

Some 3 to 6 percent of American women—3 to 8 million of them—have IC symptoms. That surprising new estimate was the biggest IC story at 2009's annual meeting of the American Urological Association (AUA), held in Chicago in April. The numbers are much bigger than most previous estimates, which should bring more recognition, research effort, and better treatments to IC.

Studies presented here also reflected new treatment approaches and showed that basic research that is beginning to tie IC theories together and point to potential new drugs for IC. New treatments being researched ranged from acupuncture and Chinese herbal medicine to immunomodulating drugs and an Alzheimer's drug related to anesthetics. Research also brought more confirmation that simple, self-help techniques—diet and urinary alkalinizers—really do help.

Kristene Whitmore, MD's state-of-the art plenary session lecture, "The Overlap between Prostatitis and other Pelvic Pain Syndromes," showed how the progress we have made in understanding both IC and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) can translate to better treatment. Important clinical and research insights have come from recognizing, treating, and researching the other chronic pain conditions that patients commonly have, such as pelvic floor muscle dysfunction, irritable bowel syndrome (IBS), and sex-associated pain and dysfunction. To treat the conditions successfully, she said, "We need to think outside the box," pointing to a new classification system, UPOINT, which will help clinicians understand what is generating patients' symptoms so they can develop better treatment plans.

The following expands on our coverage of the meeting in the spring issue of the *ICA Update* with a reader-friendly summary of every study relevant to IC presented at the meeting.

TREATMENT

Food Sensitivities Affect Men with CP/CPPS, Too

Differences in food sensitivities between female interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) patients

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The high prevalence of food sensitivity in the IC/PBS population is well documented, but little is known about it in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). These researchers compared food sensitivities in the two conditions by having 325 female IC/PBS patients and 268 CP/CPPS patients fill out a validated dietary questionnaire. The questionnaire asked about whether various dietary items and supplements caused problems and about how much of a problem they were. The responses showed that fewer CP/CPPS patients (77.1 percent) had sensitivities than IC patients (94.8 percent) did, but they had sensitivities, nevertheless. Many of the same items cause both groups trouble, with a little bit of difference in their misery rankings.

For women with IC, the top troublemakers were grapefruit juice, spicy foods, caffeinated coffee, grapefruit itself, and chili. For men with CP/CPPS, the order of the troublemakers was coffee, spicy foods, alcoholic beverages, hot peppers, and grapefruit juice. Differences also showed up in the items that made the two groups feel better. For IC/PBS patients, the top four were calcium glycerophosphate (Prelief), baking soda, and water, and aloe, whereas for CP/CPPS patients the top four were Prelief, Colace (a stool softener), Metamucil (a bulk-forming laxative), and FiberCon (another bulk-forming laxative). Men and women who had the most food sensitivities scored high on symptom scales. But there was no correlation between the rates of food sensitivity

and Hunner's ulcers, painful urination, nighttime voiding, urgency, straining to urinate, or constipation. Managing diet can help most IC/PBS and CP/CPSP patients.

Reducing Urine Acid Improves Pain, Sleep

Urine alkalization improves the problems of pain and sleep in patients with interstitial cystitis

Tomohiro Ueda, Masayuki Nakagawa, Motohiro Okamura, Hideki Tanoue, Kyoto, Japan; Naoki Yoshimura, Pittsburgh, PA

Urine alkalization really does improve symptoms, especially pain during voiding and sleep disturbance. Because high urine acidity is thought to play a role in urinary frequency and pain in IC, urinary acid neutralizers have long been used to decrease pain and other symptoms, but formal studies have never shown that approach is effective until now. This study looked at the efficacy of citrates for treatment. (Citrates are acid reducers that are taken by mouth and are often prescribed for patients who have a tendency to form kidney stones.) Fifty IC patients (male and female) took citrates for 2 to 4 weeks. Their urine pH went up (got less acid) from 5.8 to 6.2. Urinary frequency dropped from 14.5 times to 13.5 times, and the number of pain episodes went from 7.8 to 6.1 per day. Sleep/energy scores improved. Those patients who had more alkaline urine (pH of at least 6.2) had symptoms improve more, but not all measurements reached statistical significance. However, in the subgroup of patients who had pain initially, improvements were significant in urinary frequency, the number of pain episodes at voiding, sleep/energy scores, and problem index scores.

Less Botox Injected at Bladder Bottom Helps at Lower Cost with Fewer Side Effects

Intra-trigonal injection of botulinum toxin A in patients with bladder pain syndrome—results at 9-months follow-up

Rui A Pinto, André Silva, Tiago Lopes, João F Silva, Carlos M Silva, Francisco R Cruz, Paulo O Dinis, Porto, Portugal

These researchers tried a new approach to botulinum toxin A (Botox) injection for IC by injecting the lowest part of the bladder only (the trigone) rather than across the bladder wall and injecting half of the dose that's been commonly used. That cuts the cost and avoids side effects such as urinary retention. The 17 patients in the study filled out voiding charts and questionnaires one, three, six, and nine months later. Pain scores went down from 5.7 on a 10-point scale to 2.2 at one month and 1.9 at three months. Frequency went down from 17 to 8.9 at one month and to 10 at three months. The O'Leary-Sant Symptom and Problem Index scores dropped from 15.3 to 9 at one month and 6.2 at three months. Quality-of-life scores improved from 5.1 to 1.8 at one month and 0.9 at three months. Bladder volume for the first sensation of pain went up from 38 to 109 mL at one month to 110 mL at three months. Maximum bladder capacity also increased from 89 to 268 mL at one month to 326 mL at three months. Patients reported no problems with voiding, and nine months later, seven patients asked for another treatment.

Botox Plus Hydrodistention Beats Botox Alone

Comparison of intravesical botulinum toxin A injections plus hydrodistention and hydrodistention alone for treatment of refractory interstitial cystitis

Hann-Chorng Kuo, Hualien, Taiwan; Michael B Chancellor, Royal Oak, MI

At William Beaumont Hospital in Royal Oak, MI, and Buddhist Tzu Chi General Hospital in Hualien, Taiwan, investigators pitted hydrodistention alone against injections just under the bladder lining of botulinum toxin A (Botox) in 67 patients who were not helped by conventional treatment. Some of the patients got 100 U of Botox and some got 200 U of Botox, which is the dose most commonly used now. All patients who got Botox

injection had hydrodistention two weeks later. All patients took pentosan polysulfate (Elmiron) and analgesics throughout the study period.

Three months later, bladder capacity went up significantly in the 200-U group, although not in the 100-U group or the hydrodistention-alone group. However, for both Botox groups, pain scores and O'Leary-Sant Symptom and Problem Index scores went down significantly. In the hydrodistention-alone group, only symptom scores and problem scores went down significantly. Based on an overall rating of how they were doing, treatment was successful for about the same proportion of patients in the two Botox groups (from 70 to 80 percent), but success was lower for the hydrodistention-alone group (about 48 percent). Patients who got the higher Botox dose had more side effects, such as urinary retention and painful urination. Botox injection gives better results than hydrodistention alone, and the lower dose may be just as effective, which avoids side effects and reduces costs. The higher dose of Botox may make the effects last longer, but that will take further study.

Chondroitin May Make IC Bladder Surface as Impervious as a Healthy One

Intravesically applied chondroitin sulfate restores urothelial barrier function in acid-damaged bladder

Troy M Sofinowski, Paul J Hauser, David D Buethe, John A Califano, Daniel J Culkin, Robert E Hurst, Oklahoma City, OK

Chondroitin sulfate is a glycosaminoglycan (GAG), the type of molecule thought to form a protective layer over the bladder lining. Chondroitin sulfate is used in bladder instillations for IC patients in Canada and Europe. This research team worked to quantify how much chondroitin sulfate binds to the surface of damaged bladders. Binding to the damaged bladder surface was high (but not to the surface of healthy bladders). In addition, it made the damaged bladder surface as impervious as a healthy bladder surface. The findings also allowed the investigators to estimate that saturation of chondroitin sulfate might be reached in patients with a total dose of more than 200 mg.

Higher-dose Amitriptyline, Diet, Nondrug Approaches Help in Early IC

A re-look at the use of amitriptyline for the treatment of interstitial cystitis: results of an NIH clinical trial

Philip Hanno, Philadelphia, PA

The treatment trial aimed to discover whether early treatment with amitriptyline (Elavil) could give patients a better shot at getting IC under control and to see whether this might be the best first treatment. Patients who took it had this as their first IC treatment. Both they and control patients did "behavioral" therapy, such as timed voiding and diet. Patients started with 10 mg per day and took higher doses as they could tolerate them up to 75 mg per day. After 12 weeks there was no significant difference between the groups on their overall rating of how they were feeling. There were bigger differences based on other measures, however, especially for subgroups of patients who were taking higher doses. Those who were able to take at least 25 mg per day did much better than others did, with 73 percent responding compared with 53 percent of those taking placebo. Dropout rates because of side effects, such as fatigue, dry mouth, constipation, dizziness, and sleepiness, were high, making it difficult to draw firm conclusions. The improvement the researchers saw in the placebo group, however, was also encouraging, showing that there is value in nondrug approaches to IC for patients who have just been diagnosed.

Retinoid May Thwart APF Damage

Potential therapeutic effect of all-trans-retinoic acid for interstitial cystitis

Courtney Harris, Xu Cheng, Monica Liebert, Ann Arbor, MI

Because the drug all-trans-retinoic acid (ATRA), used topically to treat acne and orally to treat a type of leukemia, is known to prompt cells to differentiate, that is, take their correct mature forms, these investigators tried it in culture to see if it could bump up levels of the growth factor known to thwart the destructive effects of antiproliferative factor (APF) on bladder lining cells. The helpful growth factor is called heparin-binding epidermal growth factor (HB-EGF), and IC patients have lower-than-normal amounts in their urine. The researchers exposed lining tissue of the urinary tract to various levels of ATRA and a control substance. Normal lining cells showed a strong response to the treatment, producing up to 9-fold more HB-EGF. Pieces of tissue in organ culture also responded well. HB-EGF levels in urine from IC patients were not consistently low, but a subset of IC patients does have very low HB-EGF levels. ATRA should be explored for possible therapeutic value in IC, concluded the researchers.

APF Derivative May Block APF Damage

Inhibition of antiproliferative factor (APF) activity in bladder epithelial cells by two synthetic APF derivatives

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Derivatives of antiproliferative factor (APF) might be able to block the destructive effects of APF on the bladder lining in IC. To find out, these researchers screened a number of inactive, synthetic APF derivatives for their ability to normalize activity in bladder lining cells. Two of 30 they tried did block APF activity. More experiments are needed to determine the cellular effects and to test for drug activity and toxicity to determine which is better for development as a potential IC treatment.

Liposomes Protect Bladder Lining

Intravesical liposomal (LP08) instillation protects bladder urothelium from chemical irritation

Jonathan Kaufman, Pittsburgh, PA; Pradeep Tyagi, Michael B Chancellor, Royal Oak, MI

Liposomes, which are like tiny globules of fat, have been researched as a potential IC therapy for some time, either by themselves or as carriers of other drugs. This study showed that the liposomes by themselves act as a bladder coating to prevent injury to the lining. In contrast to rats that got just saline instillations, those that got LP08 liposomes showed mostly intact bladder linings after irritation.

Marijuana-like Drug Eases Bladder Spasms

Cannabinor, a novel peripherally acting cannabinoid-2-receptor agonist reduces nonvoiding-contractions in rats with partial urethral obstruction

Christian Gratzke, Munich, Germany; Tomi Streng, Turku, Finland; Christian G Stief, Munich, Germany; Iris Alroy, Rehovot, Israel; Thomas R Downs, Brian J Limberg, Jan S Rosenbaum, Cincinnati, OH; Karl-Erik Andersson, Winston-salem, NC; Petter Hedlund, Lund, Sweden

In this study of a cannabinoid-2 receptor blocker, bladder spasms (that don't have to do with urination) caused by blockage of the ureter went down 70 percent. Cannabinor also prevented compensatory changes in the urinary tract in the rats with obstruction, such as changes in pressure and flow. Bladder muscle from the treated rats had improved responses to carbachol (which prompts contraction) and nerve stimulation. This compound targets the cannabinoid-2 receptors, thought to play an important role in pain perception. In

addition, although this study was a model of bladder obstruction, it shows the compound has potential for other conditions with lower urinary tract symptoms, such as IC.

New Gene Vector May Help Bladder Make Natural Opioids for Pain

Effects of herpes simplex virus vector-mediated enkephalin gene therapy on bladder overactivity and nociception

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These researchers, who have been studying gene therapy applied to the bladder, tried a newly engineered virus to carry a gene. In this case, the gene was for one of the body's natural opioid painkillers. Their studies showed that treatment reduced bladder hyperactivity via opioid receptor in the spinal cord. The treatment also blocked pain responses from irritation by resiniferatoxin, a substance related to the hot-pepper substances capsaicin. Enkephalin gene therapy could be a potential treatment for urinary frequency and bladder pain in IC, said the researchers.

Memory Drug Eases Pelvic Pain

Memantine in the alleviation of symptoms of chronic pelvic pain syndrome: a randomized, double-blind placebo-controlled trial

Jordan D Dimitrakov, Boston, MA; Jean Chitalov, Ivan Dechev, Plovdiv, Bulgaria

The drug memantine (Namenda) eased pelvic pain effectively in men with CP/CPSP, hinting that it might also be effective for IC as well. Although the drug is used to improve memory in Alzheimer's disease patients in the United States, it's origin is as a folk remedy for pain in Bulgaria. The drug is derived from the snowdrop plant, which grows there. Like some anesthetics, it is an N-methyl-D-aspartate (NMDA)-receptor blocker. The trial included 170 men with CP/CPSP randomized to treatment with the drug or placebo. After six months of treatment, 77 percent of the men taking memantine reported significant improvement in pain, their overall rating of their condition, and their quality of life compared with only 16 percent of those taking placebo. The drug did not seem to affect urinary function, however. Side effects were minimal.

Chemical in Feverfew Eases Bladder Inflammation, Overactivity

Parthenolide ameliorates bladder inflammation and bladder overactivity in cyclophosphamide-induced cystitis in rats by inhibiting NF-kappaB phosphorylation

Hiroshi Kiuchi, Tetsuya Takao, Keisuke Yamamoto, Jiro Nakayama, Yasushi Miyagawa, Akira Tsujimura, Norio Nonomura, Akihiko Okuyama, Japan, Japan

Parthenolide, a potential drug derived from the feverfew plant, thwarted bladder damage in experimental animals. The compound is a natural inhibitor of NF-kappaB, which plays an important role in inflammatory disorders and may play a role in IC. Rats that got parthenolide treatment before bladder irritation showed less cell damage, a reduced increase of bladder weight from irritation, and fewer bladder spasms.

In cell culture, parthenolide suppressed features of inflammation induced by TNF-alpha. Parthenolide, said the researchers, may be a promising agent for reducing complications from treatment with cyclophosphamide, which is an anticancer drug. But the results may also mean that this has potential for IC.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Chinese Herbs May Offer Significant IC Pain Relief

The effect of Chinese herbal medicine containing aconitine on the pain relief in interstitial cystitis patients—a preliminary study

Takayuki Tsuchida, Tatsuya Miyamoto, Takashi Yamagishi, Satoru Kira, Kenji Kayanuma, Yaburu Haneda, Hideki Kobayashi, Hidenori Zakoji, Isao Araki, Masayuki Takeda, Chuo, Japan

Certain Chinese herbs that contain aconitine, a neurotoxin, may relieve IC pain. These Japanese researchers evaluated two Chinese herbal formulas, Keisika-jutsu-buto, and Mao-bushi-saisinto, in 10 patients who were not helped by other treatment. Patients were followed up for an average of about six months. Symptom scores dropped from 17.8 to 8.8. Bladder capacity rose from 51.11 to 117.78 mL. Pain scores dropped dramatically from an average of 88.0 to 13.7 on a 100-point scale. More study needs to be done, and done very carefully, since aconitine is highly poisonous, but these results are encouraging for IC pain relief.

Acupuncture Beats Standard Treatments

Success of acupuncture in the treatment of painful bladder syndrome (interstitial cystitis)

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At a clinic in England, urologists pitted acupuncture against instillation of sodium hyaluronate (Cystistat), hydrodistention, and gabapentin (Lyrica), and acupuncture won. The real test, of course, is a controlled, randomized study, and this was not, but the comparison of the treatment results from a small number of patients' records is intriguing. Fifteen patients who didn't respond to other therapies were referred for acupuncture. Before therapy, all had pain and frequency, and 20 percent had painful intercourse. Eighty percent had undergone hydrodistention, and only one (8 percent) found it beneficial; 73 percent had undergone Cystistat instillations, and only four (36 percent) thought it helped; and none of the four patients who took Lyrica found it helpful. After acupuncture, which was called "standard," all patients reported their symptoms improved, and quality of life improved for 13 of 15 (86 percent) patients. The average number of sessions needed to feel better was three, and patients experienced no complications.

DIAGNOSIS/ASSESSMENT

Classification Strategy Could Individualize Treatment

Clinical phenotyping of urologic chronic pelvic pain syndromes (UCPPS): validation of the "Snowflake Hypothesis"

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Each IC (and chronic prostatitis) patient is unique, so these doctors are working on a "phenotyping" system that would characterize patients and point to appropriate treatment strategies for each patient. The UPOINT system has six "domains": urinary (voiding symptoms), psychosocial (identifiable psychopathology), organ-specific (prostate/bladder centric), infection (history of bacteriuria/prostate localization), neurologic/systemic (associated conditions, for example fibromyalgia), and tenderness (of pelvic muscles). (The six domains are an analogy for patients' uniqueness based on six different "arms," like snowflakes.)

They then applied the system to 100 IC and 90 chronic prostatitis patients. The percentages of chronic prostatitis and IC patients who were positive for each domain were as follows: urinary 52:100, psychosocial

34:34, organ-specific 61:96, infection 16:38, neurologic/systemic 37:45, and tenderness 53:48. The more positive domains patients had, the more severe their symptoms were. Patients who had had symptoms longer also had more positive domains. Patients positive for the Neurologic/Systemic and Tenderness domains had significantly increased symptoms. These domains, along with the psychosocial domain, most strongly affected quality-of-life. More comprehensive phenotyping studies and biomarker development will further expand the domains. The UPOINT system, argued these authors, explains the consistent failure to develop a standardized treatment strategy. The system could help clinicians and researchers formulate individualized, dynamic treatment strategies.

Three Chemokines May Prove Markers for Symptom Severity, Improvement

Urine levels of selected chemokines positively correlate with lower bladder capacity and psychometric scores in IC/PBS patients

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Growth factors and chemicals called chemokines play a role in cell death and inflammatory process, such as infiltration of mast cells and white blood cells into tissue. These researchers measured the levels of some of these chemokines and tried to correlate them with symptom levels in 39 IC patients. The patients gave urine samples, filled out symptom questionnaires, and measured bladder capacity. Out of the 16 chemokines the researchers could measure, three turned out to be correlated: platelet derived growth factor (PDGF), interferon-gamma inducible protein (IP-10), and monocyte chemotactic protein-1 (MCP-1). Only IP-10 and MCP-1 showed a relationship with bladder capacity. PDGF is known to activate programmed cell death in blood vessel lining cells, and IP-10 released by lining and nerve cells seems to have the converse effect. MCP-1 is associated with activation of mast cells in bladder. Levels of these chemokines may be useful markers for the severity of symptoms and disease progression and also might show which patients could benefit from therapies aimed at the bladder.

New Pain Index Useful for IC and CP/CPPS

Validation of a genitourinary pain index for use in men and women

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In research trying to find a correlation between the urologic pelvic pain syndromes and other conditions, it may be useful to have one questionnaire to measure the degree of symptoms in both men and women, so these investigators adapted the NIH Chronic Prostatitis Symptom Index. They added two questions about bladder discomfort for men and changed the male-specific questions to female for women. Then they tested the questionnaire and found that, in men, it discriminated between chronic prostatitis and IC, some other urologic conditions, or no other conditions. In women, it distinguished between IC and incontinence or neither of these conditions. In addition, the scores showed differences in how the patients were faring. A drop of seven points helped show who responded to therapy and who didn't.

Nerve Growth Factor High in IC and Neurogenic Bladder

Increased urine levels of nerve growth factor in patients with neurogenic overactive bladder and interstitial cystitis/painful bladder syndrome

Bruce L Jacobs, Marc C Smaldone, Vikas Tyagi, Brian J Philips, Stephen V Jackman, Wendy W Leng, Pradeep Tyagi, Pittsburgh, PA

IC patients are known to have higher levels of nerve growth factor (NGF) in their urine than healthy people do. The factor might be a disease marker and might play a role in the disease. To further pin down NGF's potential usefulness as a biomarker, these researchers looked for it in the urine of IC patients as well as in the urine of patients with neurogenic overactive bladder (OAB) (the kind of OAB that occurs most often in spinal cord injured patients), OAB without a known cause, IC, prostate cancer, bladder cancer, and kidney stones. They also tested for it in the urine of healthy people and men who had had a prostatectomy. Levels of NGF were highest in the urine of IC and neurogenic OAB patients and were also high in women with lower urinary tract symptoms.

Patient Diaries More Practical than Questionnaires for Nocturia

Correlation between voiding/sleep diaries, and nocturia and sleep quality-of-life questionnaires

Tove Holm-Larsen, Bjarke M Klein, Copenhagen, Denmark; Jeffrey P Weiss, New York, NY

Patient diaries are more practical for clinical diagnosis than questionnaires for looking at nighttime frequency and sleep quality found these investigators. They looked at the relationship between the information in patients' voiding/sleep diaries and standard nocturia and quality-of-life questionnaires. The diary information and the standard measurements correlated strongly.

Dutch Pelvic Floor Questionnaire Gives Consistent Results

Development and validation of the pelvic floor inventories Leiden (PelFIs)

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These researchers tested a Dutch pelvic floor questionnaire for its ability to return consistent results. The questionnaire, with questions related to urination, defecation, and sexual function, proved to be internally consistent and also consistent over time. In addition, it showed differences between healthy people and pelvic floor dysfunction patients.

Brain Activity Differs in IC, CP/CPPS Pain

Brain activity for spontaneous fluctuations of pain in urologic pelvic pain syndrome

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Pain affects different areas of the brain in IC and CP/CPPS, showed this brain imaging study. That indicates that these two conditions are different from one another. This study even distinguished the difference in men. Patients with the two conditions underwent functional magnetic resonance imaging (fMRI) while they were having pain. They continuously rated the fluctuations in their pain, which were correlated with the activity in their brains. Brain activity maps for areas active when patients had pain showed the most active regions were in the insula in CP/CPPS patients and in the cingulate and somatosensory regions in IC patients. These regions are also different from the regions are active in patients with other chronic pain conditions, such as chronic back pain. Because the brain regions that lit up for IC and CP/CPPS patients affect decision making under stress, the investigators used some standard tests of decision making and emotional recognition and found that these skills were impaired in patients with either condition.

EPIDEMIOLOGY

IC May Affect 8 Million US Women

Prevalence of interstitial cystitis/ painful bladder syndrome in the United States

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The Rand Interstitial Cystitis Epidemiology (RICE) study developed interview questions that helped diagnose IC/PBS based on IC experts' analysis. Then, the researchers conducted a vast survey of nearly 100,000 US households, asking women about their symptoms. From that, they found that from 3 to 8 million women in the United States may have IC/PBS. That's approximately 3 to 6 percent of US women age 18 or over. This estimate is higher than many previous ones and shows that IC is truly an important public health burden.

Rate of Related Conditions Rises with Time

Phenotypic associations between interstitial cystitis/painful bladder syndrome (IC/PBS) and irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS): a case control study

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IC patients and healthy controls completed questionnaires to help researchers find out how common the overlapping conditions irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS) are and the effects on coping and social aspects of IC patients' lives. 208 female IC patients and 180 controls completed questionnaires and reported on their conditions. The prevalences reported by IC patients and controls were 38.7 percent vs 5.6 percent for IBS, 17.6 vs 1.7 percent for FM; and 9.4 vs 1.1 percent for CFS. Based on reported symptoms, the figures were even higher: 49 vs 11 percent for IBS, 59 vs 32 percent for FM, and 45 vs 7 percent for CFS.

Compared with controls, IC patients had significantly more pain, poorer mental and physical quality of life, more sleep disturbance, more stress and anxiety, more depression and increased thoughts of hurting themselves, lower perceived social support, poorer sexual functioning, and greater "catastrophizing" (feeling hopeless and helpless about the condition). Among the IC patients, 52.4 percent reported no other associated condition, 23.6 percent had only IC plus IBS, 2.4 percent had IC plus FM only, and 1.4 percent had IC plus CFS only, while 20.2 percent had multiple associated conditions. As the number of associated conditions increased, pain, stress, depression, and sleep disturbance increased while social support, sexual functioning, and quality of life deteriorated. Anxiety and catastrophizing remained high in all groups. The longer patients had symptoms, the more often they had additional conditions. The researchers concluded this indicates that there is a progression of the severity of symptoms and deterioration of cognitive and psychosocial abilities with time.

SOCIAL ISSUES

IC has Bigger Impact than Other Pelvic Conditions on Daily Life

Health-related quality-of-life impact of interstitial cystitis/painful bladder syndrome and other symptomatic pelvic disorders

Sandra H Berry, Santa Monica, CA; Ron D Hayes, Los Angeles, CA; Marika Suttorp, Santa Monica, CA; Leroy M Nyberg, Jr, Bethesda, MD; J Quentin Clemens, Ann Arbor, MI

Health-related quality-of-life in women with IC/PBS is worse than for healthy people and also worse than for other patients with endometriosis, vulvodynia, or overactive bladder (OAB). The 599 subjects in the study were IC/PBS patients drawn from the practices of 8 urologists and 15 gynecologists across the United States who are known experts in these conditions. The lowest scores in IC/PBS were for social functioning, bodily pain, and role limitations due to physical problems. These findings underscore the dramatic impact that IC/PBS has on the daily activities and well-being.

BASIC RESEARCH

Inflammation Receptor Signaling Alerted in IC

MicroRNAs mediate down-regulation of tachykinin receptor gene expression in interstitial cystitis/ painful bladder syndrome

Veronica Sanchez-Freire, Fiona C Burkhard, Urs E Studer, Thomas M Kessler, Annette Kuhn, Katia Monastyrskaya, Bern, Switzerland

A system of receptor signaling in the bladder may be altered in IC in ways that it is not in acute pain. The receptors these researchers investigated, called tachykinin receptors, are stimulated by inflammatory chemicals such as substance P and other tachykinins. Recently, microRNAs have been implicated in causing some inflammatory diseases, so the researchers also looked at whether they affected these receptors in IC patients. Their various tests show that the receptors are downregulated in IC bladders, suggesting that the receptor signaling complex is remodeled in IC patients, unlike in acute inflammation. MicroRNAs were implicated as playing a role in this, shown by the direct correlation between expression of a certain microRNA and downregulation of one of these receptors.

Proteomics Points to Bladder Lining Disruption in IC

Urinary proteomics approach to interstitial cystitis/painful bladder syndrome pathophysiology

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Researchers are starting to use proteomics—a comprehensive look at proteins—to find clues to the cause of disease or to valuable treatments. Researchers have already looked for clues in the urine of IC patients in comparison with healthy people. Now, this group of researchers has compared urine proteins between identical twins of whom only one has IC. That might help narrow the search for biomarkers to proteins that are produced only when someone actually has IC. The research identified 144 proteins significantly expressed by IC patients and not by their healthy twins. Of those, 20 (14 percent) were ones associated with pain in other studies of adults with either IC or chronic prostatitis/chronic pelvic pain syndrome. Some of those were associated with holding cells together, and others were associated with susceptibility to infections and to immunologic disease. This research team thinks that these findings fit in with the theory that the bladder lining is disrupted in IC. We may also gain other valuable insights into the disease process and identify biomarkers of disease activity from studies like these, they said.

Genes Active in Ulcerative IC Implicate Cell Signaling, Development, Inflammation

Gene expression profiles of bladder urothelium from patients with interstitial cystitis

Teruyuki Ogawa, Satoshi Seki, Tetsuya Imamura, Yasuhiko Igawa, Osamu Nishizawa, Toshiki Homma, Satoshi Akahane, Nagano, Japan; Yukio Homma, Tokyo, Japan

These researchers are hunting genes that may be responsible for ulcerative IC, which could be the clue to the cause or to potential biomarkers for diagnosing IC. They extracted RNA from IC bladder tissue and compared the level of the expression of genes between IC patients and controls. Some known markers of cells that form the bladder barrier were not expressed as much in IC tissue compared with healthy tissue. In addition, the researchers identified 564 more “probes” that were expressed at least four times more in IC tissue than healthy tissue. The top three functions of the genes implicated were cell-to-cell communication and signaling, inflammatory disease, and cellular development, including inflammation-mediating proteins such as TNF-alpha, which has been implicated in IC. These genes may be potential biomarkers for ulcerative IC.

IC, Healthy Cats Express Different Genes in Bladder Lining

Differential genes expression in urothelium from healthy cats and cats with bladder pain syndrome/interstitial cystitis

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Because cats have a disease similar to IC in humans, these researchers looked for differences in gene expression between healthy cats and those with feline IC. They found that healthy bladder linings expressed certain genes involved in making steroids and in oxidation-reduction as well as a few other genes, whereas IC linings did not. IC lining tissue expressed other genes that healthy tissue did not. These researchers will conduct more studies to validate their findings.

Mice With Bladder Lining Autoimmunity Show IC Characteristics

BALB/c-Fcgr2b^{-/-}Pdcd^{-/-} mouse expressing anti-urothelial antibody is a model of autoimmune cystitis

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These researchers worked to develop a mouse that could be used to study the nature of autoimmune cystitis. The mice showed characteristics that are thought to be typical of IC, including voiding small volumes of urine, a deficient bladder lining protein, and high levels of inflammatory chemicals (such as TNF-alpha). The reduction in urine volume occurs through bladder-specific inflammation that comes with degeneration of the bladder lining and elevated levels of inflammatory chemicals, concluded the researchers.

Pain Signaling Assumption Proves Incorrect

Distinct functional expression of Kv4 subunits in A-type K⁺ channel between bladder-innervating and somatic DRG neurons

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Potassium (K) currents play an important role in the excitability of the cells of C-fibers, nerve fibers known to carry pain signals. These researchers tested different types of nerve cells to see which potassium-channel subunits might be involved in carrying pain signals from the bladder. They found that certain subunits form a type of potassium channel in C-fibers coming from the body but not from the bladder and concluded that a potassium channel that was a potential target is probably not. It seems to be more involved in pain coming from the body than from the bladder.

MIF Blocker Prevents Cystitis

Antagonism of macrophage migration inhibitory factor prevents cyclophosphamide cystitis in mice

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A compound called ISO-1, which blocks the inflammatory chemical macrophage migration inhibitory factor (MIF), prevented bladder damage in mice. MIF plays a critical role in a number of inflammatory and autoimmune diseases, so this compound that blocks it is being researched as a treatment for a wide range of conditions, from diabetes to colon cancer. In this look at its potential for preventing bladder damage, mice were injected with the compound just before bladder irritation. The animals' sensitivity to touch on the lower abdomen and perineum was reduced, the volume of their voids did not go down, their bladders showed less inflammation, and there was no rise in the level of nerve growth factor.

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