GIBS

GLOBAL INTERSTITIAL CYSTITIS BLADDER PAIN SOCIETY

"EDUCATE, IDENTIFY, TREAT Fighting the Fire in Bladder"

Contents

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

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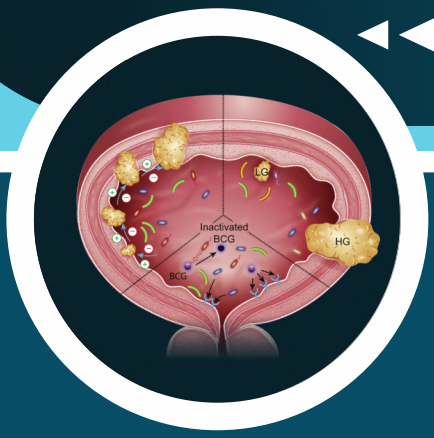
NewsLetter



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Understanding the Human Urinary Microbiome

1. Human microbiome

Microbiome are a community of microorganisms (such as bacteria, fungi and viruses) that live in a particular environment. The human microbiome is the set of genes of microorganism present in a given habitat or environment. The human microbiome matures from birth to adulthood and is critical in the development and maintenance of immune system.

The Human Microbiome project (HMP) included 300 samples, collected from the 15 - 18 specific body sites such as nasal areas, skin, oral cavity, gastrointestinal tract and urogenital tract. The urinary tract was excluded from the Human Microbiome Project. HMP found that each body site appears to have a unique microbiota, and no microbial taxa are universally present across all sites & individuals.[1]

Urobiome or Urinary microbiome

The theory that urine is sterile has been proved wrong with the identification of urinary microbiome in the healthy bladder. The female urinary microbiome (FUM) was discovered in 2011 by assessing the diversity through 16S rRNA gene sequencing.[2]

Wolfe et al used urine specimens of healthy adult women from voiding, transurethral catheterisation and suprapubic catheterisation and assessed the presence of bacteria using bacterial cultures, light microscopy and 16S RNA gene sequencing, and described uncultivated bacteria in women.[3]

It was found that each individual may have a core microbiome. The bacterial genera in women are more heterogenous and it changes with age. Conventional microbiological testing is inadequate to identify more than two - thirds of the bacteria.[4]

This healthy microbiome is thought to maintain the bladder homeostasis, by protecting against infection, promote normal immune function, neurotransmitter regulation and maintain the urothelial integrity[5].

Dysbiosis is defined as an imbalance between the healthy microbiota and the microbiota communities without the above mentioned functions[6].

This spectrum of urinary dysbiosis may help us understand the risk of clinical conditions, such as urinary tract infection (UTI), urinary incontinence (UI) and, some forms of bladder pain syndromes.

The most common urotype in the female bladder is Lactobacillus. The next most common urotypes are Streptococcus, Gardnerella, Corynebacterium and Staphylococcus. The host's hormonal status, body mass index and certain clinical conditions appear to have an influence on the FUM.[7]Urine was found to share 23.6% of species in the human gut microbiota.[8] This may be useful to understand the aetiology of some clinical conditions such as chronic pelvic pain, bladder pain syndrome.

Genitourinary microbiome(GUM) is the combination of vaginal and urinary microbiome, which is obtained from the voided urinary samples in women. It includes more than 100 species from 50 genera. The focus is to understand the relationship between GUM and lower urinary tract symptoms.[9]

Cultures methods :

Since 60 years, the Kass criterion is in use, which consists of the counting of bacteria cultured from fresh urine. Thus, the number of bacteria superior or equal to 105 CFU/ml was predictive of urinary tract infection (UTI). Therefore, the study of the urinary microbiota was unheard for a long time.[10]

Later, 562 bacteria were identified in the urinary tract, 322 were described only by culture, 139 by metagenomics &101 by both culture and metagenomics. The 8 more commonly found species in the literature were Chlamydia trachomatis, Neisseria gonorrhoeae, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, and Enterococcus faecalis . All are considered pathogenic.

As said before, standard culture techniques do not detect most species of FUM, including many uropathogens.[8]

Expanded quantitative urinary culture (EQUC) is the solution to detecting microbial species not detected by conventional urine cultures. The EQUC protocol could cultivate 80 % of the bacterial species found by 16S rRNA , majority (92%) showing no growth on bacterial cultures. The most prevalent genera isolated were Lactobacillus (15%), followed by Corynebacterium (14.2%), Streptococcus (11.9%), Staphylococcus (6.9%) and Actinomyces (6.9%). Other genera commonly isolated include Bifidobacterium, Aerococcus, Gardnerellaand Actinobaculum, which comprise the resident female urinary microbiota.[11]

Metagenentics

The whole genome sequencing can be performed as a form of next generation sequencing (NGS), DNA NGS is generally performed using polymerase chain reaction amplification and 16S rRNA gene high-throughput sequencing, which allows the entire genome to be sequenced. Limitations of NSG are -

1. expensive
2. not widely available
3. inability to distinguish closely related bacterial taxa, confirm bacterial viability, and link the genotypic resistance to a specific organism.[12,13]

Ideal technique to collect urine sample Transurethral catheterisation is considered an optimal technique to collect urine as it lowers contamination of clean catch voided sample, and is less invasive than the suprapubic technique of urine sample collection[8]

Impact of urine microbiome in Bladder pain syndrome A recent review found that research regarding the impact of urinary microbiome on interstitial cystitis/ BPS and lower urinary tract function is in the preliminary stages, with four out of five studies finding no association between the urinary microbiota and IC/BPS. Evidence on the role of lactobacilli on bladder homeostasis are inconclusive, and need further research. In patients with IC/BPS, it is found that lactobacilli urotype is present in mainly premenopausal age and absent in the postmenopausal age.[13]

Testing for IC/BPS is unfortunately extremely limited because 16S NGS is unable to detect eukaryotic microbes, and EQUC cannot identify several types of fungi, resulting in many negative tests using the current diagnostic standards due to culture testing inconsistency.[14,15]

Our understanding of the urinary microbiome The urinary and vaginal microbiome are related and most likely to influence each other. The urinary microbiome has a low biomass. Similar strains of uropathogens are found in the urine and the vagina of females. The presence of healthy microbiome is associated with lower use of anti - cholinergic in women with LUTS and presence of certain bacteria such as Lactobacillus crispatus is associated with absence of LUTS, owing to the healthy bladder.

Current research shows that the microbiome of the bladder does not impact on IC/BPS.[16]

Antibiotic therapy affects the inherent urinary microbiome. Dietary and lifestyle changes influence the microbiome.

Conclusion

Further research is warranted in understanding the urinary microbiome in Indian subcontinent, as our lifestyle and dietary habits are different from the western counterpart.

The upcoming research on the microbiome and the use of probiotics is exciting. With WHO declaring antimicrobial resistance(AMR) as a global threat, the commonest indication to use antibiotics is a UTI. The understanding of urinary microbiome may help to decrease the burden of AMR.

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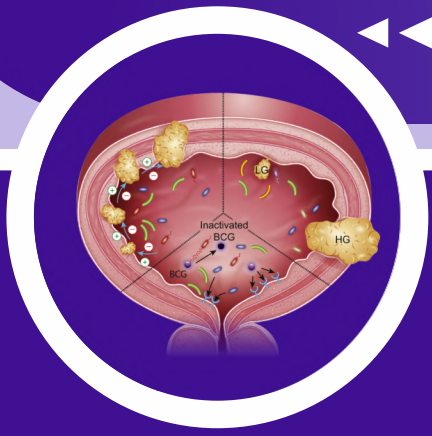
GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

VOLUME 4, ISSUE 2 (SUPPL) (FEBRUARY 2022)

NewsLetter

Supplement



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"BOTOX" in the game: Tips and Tricks in Interstitial Cystitis/Bladder Pain Syndrome

We at Swati Spentose Pvt. Ltd, in 2016 had taken up an initiative to bring about awareness in Interstitial Cystitis!!!

&

We are still going strong and believe to continue going stronger and stronger with every passing year…

> "He who has health, has hope; and he who has hope, has everything!!!"
> - Thomas Carlyle

Interstitial Cystitis - This has to STOP!!!

Have you ever thought of a feeling of sudden urgency to void with severe pelvic pain?... Be devoured by the feeling???...

Dr. Sanjay Pandey, the Head of Department of Urology, Gender Reassignment and Renal Transplantation at Kokilaben Dhirubhai Ambani Hospital, Secretary of Global Interstitial Cystitis Bladder Pain Society (GIBS) focused on tips and tricks for using Botulinum Toxin A in pelvic floor spasms, vaginismus or IC/BPS for patients

who are suffering… who are in agony… in case of flare ups and reduce the number of hospital visits in an attempt to improve the quality of life of these individuals.

Earlier, Botulinum Toxin A was proven and taken up by USFDA for upper limb muscle spasm spasticity. Later, in 2011 Botulinum Toxin A came up in Urology after FDA approval for refractory Vaginismus exhibiting pelvic floor spasms. Pelvic floor therapy was too one such scope aiming to treat pelvic floor spasms or pelvic floor dysfunction.

The pelvic floor cavity allows women to have a coitus, which was impossible in patients with vaginismus and probably all kinds of physio or psychotherapy which could actually help them, was found adrift in their refractory vaginismus.

This condition provoked Dr. Pandey to come up with a thought of some tips and tricks and he, later shared his idea about tips and tricks in use of Botulinum Toxin A.

Botulinum toxin A injections are in powdered form, completely invisible, settled down at the bottom of the vials in frozen state. The Botulinum toxin A injections are very expensive and hence, mishandling must be avoided. Mishandling must be avoided during reconstitution as every drop matters. Passage and formation of air bubble inside the vial must be avoided. The vial must be restricted from shaking. The vial is vacuumized and hence minor shake may lead to formation of air inside it which can't be proceeded with, to be injected both in the muscles or in the bladder.

The injections must be injected under general anesthesia with a spinal needle during refractory conditions where medicines and pelvic floor therapy has been a failure. The finalized dose may be 100 or 200 units. 200 units are generally recommended for deep muscle pelvic floor. The amount of pelvic floor spasm is best associated and evaluated under local examination and the final trigger points are re-evaluated and the site of injection is finalized. Locating the area for injection is one of the most important facets and needs pre-evaluation, as Botulinum Toxin A injection on wrong site may lead to fecal as well as urinary incontinence. Hence, the worrisome surfaces of vagina for injections are anterior and posterior surfaces. This might impact the neighbouring organs as well i.e. the rectum and the urethra and one definitely end up with diminutive incontinence.

Thorough understanding of the pelvic floor is essential which helps to locate the best suitable site for injecting Botulinum toxin A injections. Lateral, posterolateral, anterolateral are the most suitable sites for Botulinum Toxin A injections under general anesthesia and makes the procedure well tolerable and the injections last in pelvic muscles and the skeletal muscles for next three to five months compared to the bladder where traditionally the injections would last for six to nine months. The technique may even probably allow to be effective for 9 to 12 months. But in the skeletal muscles one may have to come back after 4 to 6 months or even 6 to 9 months as required. Depending upon the effect or efficacy the next visit is being decided.

Hence the tips and tricks follow a finalized set dose of 100 to 200 units, with general anesthesia and avoidance of formation of air bubbles with Injections in lateral and posterolateral regions of the pelvic floor and the procedure is done successfully.

Presenter

Dr. Sanjay Pandey

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The Blog is written by Dr. Sapna Biswas [Scientific Writer - GIBS] while it was presented by me at GIBS 2021 6th Annual Conference on IC/BPS.
- Dr. Sanjay Pandey

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

VOLUME 4, ISSUE 3 (MARCH 2022)

NewsLetter

High-tone Pelvic Floor Dysfunction with Bladder Pain Syndrome

Introduction

High-tone pelvic floor dysfunction (HTPFD) also termed as hypertonicity of the pelvic floor musculature, nonrelaxing pelvic floor dysfunction, pelvic floor spasm, or myalgia of the pelvic floor. It is identified in a patient of Bladder Pain Syndrome (BPS) by presence of tender and hypertonic pelvic floor and associated musculature. This could be responsible for irritative and/or obstructive voiding symptoms and/or pelvic pain [1] in approximately 80% of BPS patients [2]. Its clinical importance stems from symptoms that may extensively overlap with BPS, making diagnosis of both conditions more challenging.

Etiology

The exact cause is not known, but may represent an aggravation or unmasking of hidden childhood voiding dysfunction [3], where BPS and HTPND both are primary pathologies but their co-existence can worsen the overall symptomatology. Some authors suggest that cross-talk through viscerosomatic and visceroviscereal neural pathways may play a bidirectional role in the development of IC/BPS and HTPFD [4]. Presence of altered activity and connectivity of pelvic floor sensorimotor cortical control regions in female patients of BPS on resting state functional MRI, indirectly support this theory [5]. Other etiologic consideration which can explain its presence as secondary to BPS include its development as guarding behaviour in response to bladder pain. Simultaneous presence of dyspareunia and painful defecation with typical worsening of symptoms of all these three organ systems during flare of BPS; strongly suggests this etiology.

Diagnosis

History

This condition usually present with *symptoms* like pelvic/perineal pressure, persistent urgency, the sensation of incomplete bladder emptying with interrupted poor flow in severe cases, urinary hesitancy (straining or use of abdominal pressure to initiate or

complete voiding), need to sit for prolonged periods on toilet seat to evacuate the bowel and /or the bladder completely, constipation, dyspareunia (pain often experienced the next day of intercourse), and perineal, penile, and ejaculatory pain in males. The clinical diagnostic dilemmas generated by the presence of HTPFD include its ability to generate pain alone or in association with BPS, and the overlap of symptoms between these two conditions. The associated irritative symptoms may be confused for Overactive Bladder. HTPFD may also be responsible for complaints associated with other pain syndromes such as chronic prostatitis/chronic pelvic pain syndrome [6] and vulvodynia [7].

Examination

Physical examination should include a detailed palpation of the pelvic floor musculature and adjacent musculature.Hallmarks of HTPFD include the presence of hypertoniclevatorani (on Modified Oxford Grading system) with simultaneous spasm of nearby accessory musculature, muscle banding, and myofascial trigger points.The latter being described as tender "knots" in taut muscle band that produce pain on palpation[8].The studies suggest thatoverall myofascial trigger point can be identified on pelvic floor examination in approximately 78% of BPS patients, while multiple trigger points can be identified in 68% of individuals [2].

Investigations

Although not essential for diagnosis, video urodynamic evaluation will demonstrate poor relaxation of the external sphincter [9] in almost 70% to 94% of IC/BPS patients with HTPFD.

Treatment

The co-existence of HTPFD will either magnify the pain of BPS, or it may be the sole cause of symptoms. In both the cases, failure to diagnose HTPFD in the presumed BPS patient will commonly lead to a suboptimal response if we follow the typical algorithm of management strategies for BPS as suggested by many guidelines. The obvious reason is that treatment strategies differ between the two conditions. Therefore the treating clinician should be particularly concerned about the presence of HTPFD in the patient who endorses a history of dysfunctional voiding, bowel disturbances, and sexual pain; especially once the bowel and bladder disturbances originated in childhood [3]. On suspicion of HTPFD, a physiatrist/trained physiotherapist must be involved. The following multidisciplinary approach may be helpful to ameliorate symptoms [10]:

1. Behavior modification (avoidance of straining maneuvers, "reverse Kegels," stress reduction),
2. Topical heat application
3. Oral Medications e.g. skeletal muscle relaxants apart from selective use of pain killers
4. Control of constipation
5. Anesthetic or botulinum neurotoxin type A (BTX-A) injections at myofascial trigger point or affected muscles[11]

Conclusion

The common presence of systemic and regional pain conditions like HTPFD along with BPS is responsible for the complex presentation of this condition and to get a typical bladder-centric patient of BPS is actually rare in clinical practise. Therefore an individualized strategy of care will ultimately benefit these patients.

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GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

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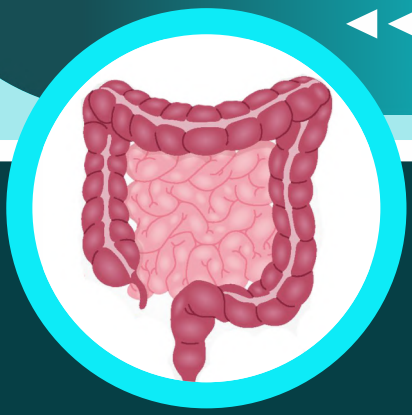
NewsLetter



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"The Gut Microbiome- A Necessity for GOOD HEALTH"

What's on Your Platter.... Green Salad

Well… Let's nurture the Gut Microbiome too…

It's Spring (Vasant season) in India, and I have been these days feeling awesome and energetic. As if the love hormones, the dopamine, oxytocin gushing through my blood with full energy making me enthusiastic about writing this article. Feeling the positivity all around me, as if it is a new beginning. Yes! indeed… spring is all about a new beginning, blossoming of fresh buds, the dawn chorus of finches and that's when I felt, the most hated, the most cursed life on the planet earth; "the microbes"too needs to be loved, nurtured, and cherished.What provoked me to feel this way?... Last night while I was watching this video by Dr.Shivam Priyadarshi,Core Member GIBS (Global Interstitial Cystitis Bladder Pain Society) and Senior Professor and Head of the Department of Urology, S.M.S Medical College & Hospital in Jaipur, India;He emphasized how some micro-organisms help us, support us and nurture us to overcome our health problems. Not all micro-organisms are bad, there are good ones too; just the way it is said,

> "Don't forget that the flavors of wine and cheese depend upon the types of infecting Micro-organisms"
>
> *-By Martin Fischer*

Since time immemorial our spiritual masters and saints preached, that we are not just physical body that can be seen with naked eyes or the mind and brain that feels and thinks, but we have microbes residing in and on our body that are 10 times more than the total number of human cells. The genetic composition of microbes amounts to a stupendous 3 million genes which is 300 times more than the human genome .There are more than 1,000 species of bacteria which controls almostall the bodily functions. Around 80% of our immune system is in microbiome and 90% of chemicals like serotonin which is responsible for a sense of well-being come from micro-organisms. Our body isonly 10% human cells while the rest 90% is microorganisms. And… "when the Gut Microbiome is balanced, one feels healthy, happy, and energetic". Suddenly, I realized that the reason for my happiness, romantic and energetic feeling… lies in my gut microbiome which is playing a crucial role in my body. Thanks to my gut microbiome…

Wonder… How do these microbes enter the human body???

The entry of these microbes in the human body (skin, mucous membranes, upper respiratory tract, the GI tract, the urinary bladder, the urethra the external genitalia, vagina, ear canal and external eyes) is via. four stages of development from the foetal stage to the adult stage. During the foetal stage of development, the gut is usually sterile, but during a normal delivery the baby acquires bacteria from the vagina of the mother, the faeces and the hospital environment. Later in the developmental stage, the human body (baby) acquires different microbiome fromdifferent modes of feeding. i.e. breastfeeding or bottle-feeding. Breastfeeding gives more of *Bifido* bacteria, while bottle-feeding gives *Bacteroides* and *Clostridial species*. The flora changes as weaning starts with solid food and gradually it acquires the adult flora.

After the Human Genome Project in 1990, the Human Microbial Genome Projectis the new study where samples taken from the different sites of the human bodyi.e., the nasal passages, oral cavity, skin, GI tract and urogenital tract have shown their contribution to survival of humans, more than the human's own genes.The bacterial protein coding genes are 360 times more abundant than human genes and provides support in almost all functions of the body. They enhanceability to harvest nutrients, help in digestion, absorption, fermentation of carbohydrates, break up the pectin and starch into butyrate and acetate which helps to keep the intestinal epithelial lining and prevent inflammatory bowel disease. They produce vitamins like folic acid and biotin, produce additional energy, provide resistance to development of tumours and cancer. They assist in developing a mature immune system andprevent allergies. They prevent colonization of pathogens and antagonize other pathogenic bacteria by producing short chain fatty acids, bacteriocins and peroxidases which kills or inhibits pathogenic species. Gut microbes also stimulate development of intestinal epithelial cells, lymphatics and capillary density. They prevent infection by producing cross-reactive antibodies.

Gut microbes also helps to reduce stress. It impacts the nervous system by triggering the HPA Axis (Hypothalamus Pituitary and Adrenal Axis). A neurotransmitter known as GABA is produced by these gut microbes such as *Lactobacillus* and *Bifido* bacterium. Gaba neutralizes the over excited neurons and present a state of relaxation in the body.

Generally, we consider the colon to be metabolically inactive, but the colonic microbiome has mass almost equal to one kidney, and is metabolically as active as the liver. It produces 20 to 70 g of carbons, 5 to 20 g of protein per day and over 100 kilocalories per day. A skewed gut microbiome i.e. dysbiosis influences various disorders associated with the nervous system like autism, depression,anxiety, allergic problems like asthma, causeshypertension, ischemic heart disease, peripheral vascular disease and a major contributor of obesity, metabolic syndrome, inflammatory bowel disease and colon cancer.

A diet high in processed food and sugar, conventionally raised meat and dairy products which are full of hormones and excessive amounts of antibiotics, antacids along with chronic stress are the common sources of dysbiosis (imbalance in microflora) leading to impaired gut health. The increasing number of Caesarean-sections, the present trend of formula feeding instead of breastfeeding are an add on..contributing to an impaired gut microbiome state in new born and children .Hence, a healthy gut microbiome plays vital role in preventing various diseased conditions of the human body.

In a study of the role of gut microbiome in Interstitial cystitis/Bladder pain syndrome(IC/BPS)the large gut wasfound to influence the urinary bladder. Both the visceral organs are embryologically same in origin,developing from the cloaca, positioned close to each other in the pelvis on the same pelvic floor muscles and a joint peripheral innervation co-ordinate their function of storage and excretion of faeces and urine. Hence, urinary bladder and large bowel interacts via various cross reflexes.The cross talk and cross sensitization of the triad of brain, bowel and bladder may result in a multiple bladder bowel dysfunction and gut microbiome is considered to play a major role .

Few case-studies discussed here, emphasize the role of gut microbiome in the treatment and management of IC/BPS. On studying the class of microbiomes in IC/BPS and control samples, 26 significant features of microbiome were found in IC/BPS patients compared to controls and were more frequent in IC patients versus the control. As a corollary to this studyanother study showed thatthe stool-based biomarkers can be used for diagnosis of IC/BPS.

It is not just the gut microbiome, but the urinary microbiome also has a role to play and the dogma that urine is sterile in healthy individuals, no more holds true.The "Next Generation Sequencing" and extended quantitative cultures are the tools to prove that even the normal healthy urine has hundreds of species of bacteria of which 2/3rd is shared from the gut and 1/3rd from the vagina in females.Alterations and variations in the urine microbiome (abundant *Lactobacillus*) was noted in patients with IC/BPS compared to normal controls. Besides, the urinary microbiome, it is the vaginal microbiome which affects the symptoms of women with interstitial cystitis. Increased level of proinflammatory cytokine in women with IC/BPS was also a factor for developing IC/BPS.

In post menopausal women change in the vaginal environment causes symptoms of IC/BPS and use of exogenous estrogen cause changes in this vaginal environment by promoting Lactobacillus in vaginaA study showing the relation between interstitial cystitis and recurrent urinary tract infection (RUTI), chronic use of antibiotics (may change the natural vaginal microflora and may exert adverse effect) exhibited the potential role of the urinary microbiome in the pathogenesis of IC/BPS. It has been shown that alterations in the natural microflora may contribute to pain and voiding dysfunction in IC/BPS patients.Such alterations in vaginal microbiome may foster uro-pathogen reservoir expansion and may result in recurrent infections in these patients.

MAP research network which is a multidisciplinary approach to pelvic pain is a flagship study of N.I.D.D.K. In this study ,on analysis of patients of interstitial cystitis with their microbiome, overabundance *Lactobacillusgasseri* and low prevalence of *Corynebacterium*was seen. The study also showed the difference in microbiome in uncomplicated cystitis and interstitial cystitis patients. The study suggested that direct sampling of the bladder tissues would be more helpful than taking samples from the bladder surface or from the urine in diagnosis of IC.

One of the latest studies published in June 2021,showed that the bacterial microbiota of the inflammatory subtype of IC (Hunner's Lesions) is likely to be more associated with a specific bacterial species or amicrobial pattern rather than the non-hunner's variety of IC/BPS.

In spite ofstrenuous work afloat in this field, there remains many unanswered questions.

What is the impact of the bacterial flora during the flares of IC? Do they change or achieve normalcy during period of remission?

We know that *F.prausnitzii*, the good bacteria in colon that producebutyrate is useful to prevent inflammatory bowel diseases.Does the bladder lacking such good bacteria leads to breakage of the uro-epithelial barrier resulting in interstitial cystitis.

If diagnosis of IC is possible with a simple stool test by estimation of bacterial and fatty acid metabolite levels and if excessive use of antibiotics can be a contributing factor in IC, whether the restoration of existing bacterial levelsimprove the symptoms in IC patients…
In one such study, intravesical instillation of *Lactobacillus rhamnosus*was found to be a very safe and well tolerated particularly in adults and pediatric patients with neurogenic lower urinary tract dysfunction and IC/BPS. Faecal microbiota transplantation is now a highly proven effective treatment for patients suffering from Clostridium difficile infection led pseudomembranous colitisand liver disease .

Along with all the above-mentioned techniques, there exist agencies which actually analyze the gut microbiome of an individual to recommend a personalized prebiotic, probiotic and a dietary regimen for management of dysbiosis.

So, to conclude, it is just the beginning of Gut microbial research .Microbiomes contribute to the pathogenesis of IC/BPS directly by supplying uro- pathogens or indirectly through organ crosstalk dysfunction. The extended research and studies may have very far-fetched results which can radicallychange the way IC/BPS is dealt with. The gut microflora by their genes, by-products and metabolic activities influence human metabolism, immunity, health and diseases. Manipulation of the gut flora may be an integral part of different disease treatments in future.

Knowing the IC microbiome is essential may help us to accurately diagnose IC/BPS and might lead to new treatments that are directly targeted at organisms known to be prevalent in IC microbiome.

Thanks to the millions of microbes present in the gut and the body, which take care of ourselves in health and disease. So, hereafter I will definitely take care of my gut microbiome to keep me healthy and infuse happiness and energy in me.

Presenter

Dr. Shivam Priyadarshi
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GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

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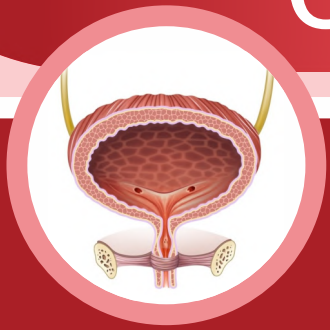
GIBS News Letter



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UNDERSTANDING SYMPTOMS OF IC/BPS

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic debilitating condition of unknown aetiology. It is characterized by persistent pelvic pain with lower urinary tract symptoms. The pathogenesis, as to which mechanisms perpetuate inflammation, remain unknown. It is potentially associated with urothelial malfunction and neurophysiological dysfunction. IC/BPS frequently presents with somatic and/or psychological symptoms, that commonly result in central nervous sensitisation. Typically, the condition is characterized by persistent pain perceived to be related to the urinary bladder in conjunction with urinary frequency and/or urgency. Obstructive symptoms such as slow stream, dribbling and straining are also often reported by painful bladder syndrome and interstitial cystitis (PBS/IC) patients.

SUBTYPES

IC/BPS can be categorized into two subtypes at present: (i) IC/BPS with Hunner lesions, which is also known as the ESSIC BPS type 3; and (ii) IC/BPS without Hunner lesions, which includes the ESSIC BPS type 1 and 2. These two subtypes, which are distinguished simply by the cystoscopic presence or absence of Hunner lesions, present with different, but overlapping, clinical characteristics and cannot be clinically differentiated in the absence of cystoscopic findings.

ONSET OF SYMPTOMS AND DISEASE EVOLUTION

IC/BPS presentation can vary from being a relatively mild disease to a severe progressive disease ending up in a small shrunken bladder. Some patients of IC/BPS have rapid onset of their symptoms and fast clinical progression. This suggests that IC/BPS comprises a heterogenous group of triggering and perpetuating factors with different diseases merging into one common clinical pathway.

IC/BPS with Hunner lesions is characterized by an older age at diagnosis, more severe bladder-centric symptoms, reduced bladder capacity, fewer comorbid non-bladder conditions and more favourable outcomes on endoscopic treatment compared with IC/BPS without Hunner lesions. IC/BPS without Hunner lesions is frequently accompanied by non-bladder symptoms, including other common systemic pain problems ("bladder-beyond" pain), psychosocial health problems and affect dysregulation. Recent studies have shown that these clinical characteristics of IC/BPS without Hunner lesions strongly overlap with those of widely known somatoform disorders or functional somatic syndromes (FSSs), such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome and migraines.

SYMPTOMS OF IC/BPS URGENCY

Urgency is defined as "the complaint of sudden compelling desire to pass urine, which is difficult to defer". In IC/BPS urgency is primarily reported because of pain, pressure, or discomfort. This is different from overactive bladder (OAB) where urgency is there for a fear of leaking urine. Bladder pain is rare in patients of OAB. However, it is important to remember that both conditions can co-exist in a patient. 40% of women with OAB also report urgency because of pain, pressure, or discomfort.

PAIN

Urothelial denudation is a characteristic histological feature of IC/BPS with Hunnerlesions. Specifically, full layers of the urothelium are frequently sloughed off at Hunnerlesion sites. This entire loss ofthe urothelial barrier at lesion sites could permit urinary stimuli to directly come into contactwith afferent peripheral nerves in the bladder. This could be one possible explanation for thehypersensitive bladder symptoms; that is, occasionally susceptible to the change in urinecomposition in patients with IC/BPS, as consumption of specific diets exacerbate thesymptoms. Pain is described as located in suprapubic, urethral, vaginal, perineal and low back regions. In a case-control study of IC/BPS, 92% patients reported perceiving one or more bladder or LUTS (lower urinary tract symptoms). 41% noted a bladder location of pain, 34% noted pain on bladder filling and /or decreasing with voiding, 17% mentioned other urinary tract symptoms and 8% noted only non-urinary symptoms.

Another study looked at whether patients of IC/BPS also demonstrate characteristics of visceral pain syndromes. The authors observed that IC/BPS patients also demonstrate discomfort at other sites besides the suprapubic region.

VOIDING DYSFUNCTION

Obstructive symptoms such as slow stream, dribbling and straining are often reported by IC/BPS patients. Cameron and Gajewski studied 274 patients who met the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) research definition of IC. Those who had completed pressure-flow urodynamic studies (UDPF), a urinary symptom score and had a cystoscopy with hydrodistension, were included. All patients had both cystometry and pressure-flow studies. The cut-off values of maximum flow rate (Qmax) 12 ml/sec and detrusor pressure at maximum flow (PdetQmax) 25 cm H2O were used to define BOO in these women. They observed 48.1% of their patients with IC/BPS have symptoms of bladder outlet obstruction (BOO). Detrusor Overactivity (DO) can be seen in upto 15% of patients with IC as demonstrated by the IC database study group. The exact mechanism of this is not well understood, but there is a possibility of stimulation of afferent nerves and detrusor muscle by both neuronal and non-neuronal-sensorimotor factors acting on bladder urothelium.

BPS AS A SOMATOFORM DISORDER

Growing evidence suggests a potential connection between IC/BPS without Hunner lesions and somatoform disorders. Somatic symptoms could be linked to biological pathways that increase the risk of IC/BPS without Hunner lesions. A study that carried out MRI of the brain of patients with UCPPS and fibromyalgia, and pain-free controls showed similar abnormal brain activity in patients with UCPPS and fibromyalgia.

The relationship between specific dietary intake and symptom changes is commonly seen in IC/BPS and FSSs, in which some dietary metabolites might act as excitatory neurotransmitters, resulting in the central nervous sensitiSation. These findings suggest that IC/BPS without Hunner lesions might share its pathogenetic neurophysiological process affecting the CNS with somatoform disorders or FSSs. The underlying pathophysiology of FSSs remains unclear, but aberrant neuroimmune or endocrine processes with

certain stressors might be responsible for central nervous sensitization and systemic hypersensitivity.

SUMMARY

IC/BPS refers to a symptom syndrome complex characterized by persistent pain perceived to be related to the urinary bladder in conjunction with urinary frequency and/or urgency, and maybe associated with voiding dysfunctions. There are certain critical differences between IC/BPS with and without Hunner lesions. IC/BPS with Hunner lesions is an inflammatory disease of the urinary bladder potentially associated with enhanced immune responses and infection, whereas IC/BPS without Hunner lesions is a non-inflammatory disorder with little evidence of bladder etiology. Categorization of IC/BPS based on cystoscopic (and histological) examination at initial diagnosis determine each subtype may change the management. For example, local fulguration and steroid injections, intravesical instillation of DMSO, and cyclosporine A administration are likely to improve patients with Hunner lesions. In contrast, neuromodulation therapy and/or a multidisciplinary treatment management of related somatoform disorders are more likely to be effective forpatients with IC/BPS without Hunner lesions. Tailored approach in this manner and could lead to better outcomes in clinical management and future research of IC/BPS.

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GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

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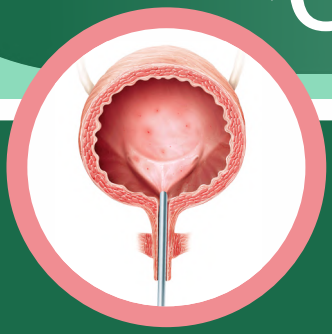

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Intravesical Injections.... Hope In The Horizon!!!

> **Hope Is...**
> **Being Able To See,**
> **That There Exists A LIGHT...**
> **Despite All The**
> **DARKNESS!**

It is summers and every single life on this planet earth is eagerly waiting for monsoon to approach. Summers is nearing end and every life is desperate to feel the gentle, fresh, cool wind blowing through their hair with wet sprinkles of rain covering their face. This is nothing but a hope to witness transition from heat to cold, and so monsoon is always a season where people feel "love is in the air". Similarly, with a hope of being able to reduce some of the sufferings of the IC/BPS patients, Prof. Rane, Chair, and Head of Department of Obstetrics & Gynaecology at JAMES COOK UNIVERSITY and Consultant Urogynaecologist at The Townsville and Mater Hospitals, Townsville, Queensland has conceived this idea of using a unique technique; a cocktail of intravesical injection for interstitial cystitis/bladder pain syndrome, which is a condition of unknown etiology with symptoms of urinary urgency, frequency, and severe bladder pain on filling up. Prof. Rane has focused more onto the pain and pain management obviously with a hope, that these

techniques will ease out the pain and agony of a greater number of patients suffering out there.

Aristotle once quoted “Hope is a waking dream”, and I feel an IC patient who is continuously wayfaring through journey of suffering and pain, constantly hopes for their gut-wrenching journey to cease. During the annual GIBS meeting Prof. Ajay Rane, was invited for a talk on some of his experiences using one such intravesical injections for IC/BPS. IC/BPS is a widespread problem, underdiagnosed, underappreciated and patients wander from pillar to post, surgeon to surgeon with a hope of end, to their condition. The worst a patient feels is when they are told, it's all in their head and referred to some psychologist and tagged under the category of mental illness or psychopath. After listening to Prof. Rane's talk, it was clear that, the most important criteria (symptom) for IC/BPS, seemed to be the bladder pain, more precisely … the “Filling Bladder Pain”. No pictures of Cystoscopy or no reports show such distinct condition of IC/BPS as it is shown by bladder pain, and Prof. Rane's technique, was predominantly for Bladder Pain and not for urgency, frequency or nocturia. IC/BPS is a pathology of uncertain etiology. It may be related to ruptured GAG layer, an auto-immune condition may be a reason too, any childhood untreated urinary tract infection, or there may be a neurogenic element to it. He feels infective element to be a very interesting concept in IC/BPS as there is a rise in the number of populations becoming aware of the urinary biome, the vaginal biome, and the change in the biomes when infection or inflammation sets in. This very well correlates with mast cell activation. He discussed one of his thought processes that highlighted the connection between the Metabolic Syndrome and Painful Bladder Syndrome. A fasting glucose tolerance test was done on a big cohort of his patients, and it was found that, despite the Hb1ac normal and the random blood sugar normal, 56% of the patients had impaired glucose tolerance of full-blown type II diabetes. He feels this option of association of metabolic syndrome with painful bladder syndrome is not yet explored and needs to be explored. He further focused that, the intake of refined foods, lack of fasting, obesity and metabolic syndrome plays a huge role in painful bladder syndrome. Different evidence-based management of IC/BPS are lifestyle modification with acid free diet, stress reduction (meditation, mindfulness yoga and exercises), bladder retraining, timed voiding may be followed. Medical treatment available for the management of IC/BPS is antihistamines, Cimetidine, Amitryptiline, hydrodistensions, bladder instillations and neuromodulations which is extensive as well as expensive. However, Prof. Rane focused on use of intravesical injections which is done by blabbing the sub-mucosa with 3-5 ml of a cocktail solution, not as deep as the BOTOX, but superficial just underneath the mucosa. A five-year retrospective data was discussed by Prof. Rane. The study included 408 patients treated with 647 episodes of intravesical cocktail (Triamcinolone/bupivacaine/gentamicin) injection. This cocktail injection was precisely for pain, and not for frequency or urgency, which is an important concept to remember. The demographics of the patient showed their mean age to be 61.2 years which tells that, patients wait for a long time before they present to the care givers or doctors. He clearly mentioned this is not that, this is a condition of people in their 5th and 6th decade and this condition was in his youngest patient of 14 years of age. So, this condition is poorly understood and managed, and patients wait for a long time before receiving a positive therapy. All the patients received entire gamut of conservative treatment including lifestyle modification and medications and finally were moved on to the tertiary treatment of bladder installation, bladder injection or sacral nerve stimulation. It was seen that of the total patient population 64.7% of women and one man needed only one treatment with good control of symptoms, especially pain, 22.7% received two treatments and 5% a small cohort of patients received more than three treatments because they kept coming back because they feel better. Prof. Rane mentioned it very focused and clear, that any patient who doesn't feel better with the treatment won't keep coming back to the doctor. Despite, of mentioning that such intravesical injections can't be given more than three times a year, patient kept coming back to continue feeling good pain free.

In severe cases, it was noticed that the bladder capacity was increased with the cocktail and rotational treatment between BOTOX and intravesical cocktail injection too was given. Botox is generally given deep inside, whilst the intravesical cocktail injection is given as a bleb uplifting the epithelium. So, it is important to understand the efficacy and interval between the two treatments. It was seen that, 87% of patients were at

symptom control within two treatments, those patients who required more than two treatments did so at progressively shorter levels. Such results indicates that, the patients have become pain free, and the moment the pain comes back, patients need their injection back again. It's almost like drug addiction. A weak correlation was noted by Prof. Rane between increasing age with response to the cocktail treatment. The correlation was "the older you get, the better you respond" and absolutely zero major complications were associated with the intravesical cocktail treatment. Hence, the conservative measures should be first line Some amazing emerging therapies such as the use of sildenafil, another drug that basically theorized to inhibit potassium release, thereby preventing mast cell degranulation. There are also some mast cell stabilizing medications which contains lots of side effects. Cannabinoids is considered a future hope to reduce IC considerably. Novel intravesical drug delivery system, where a drug can be embedded in liposomes, electro motive drug administration, reverse thermal gelation hydrogel. Some of these techniques may be used in creation of a new mesh to put in the vagina problems. Lidocaine releasing intravesical gel, hyperbaric oxygen therapy, extracorporeal shock wave therapy are few others in the line. Prof. Rane emphasized on the latest, and commonly used technique of roller ball diathermy to the Hunner's ulcers. It has been seen that, biologists are extremely keen to use this solo technique, especially where there has been a need in prostate. But it was found that, if a patient has Hunner's ulcer, it may be injected as much as one want. They tend to remain there or recur. If the hunner's ulcer are diathermalize with a roller ball, the frequency of recurrence reduces drastically and may recur in a different site, however the pain subsides. So, the whole idea behind the talk session was to see whether one can manage the pain associated with IC/BPS. Use of a diathermal roller ball is a last desperate line of treatment. Hence, this is a therapy which is available and can be used quite easily without any complications, especially for the pain part of the painful bladder syndrome. In summary, Prof. Rane mentioned the fine details of the intravesical cocktail injection. The intravesical cocktail injection consisted of two ampules (8 mg) of triamcinolone, with 20 ml of 0.25 marked with adrenaline and sometimes 80 million Gentamicin is added to the cocktail. A special needle is used for the intravesical injection called as BoNee by Coloplast used for Botox injections too. Also, a delivery system is used, that allows to bleb the mucosa of the bladder supra trigonally. These were few of the points to be noted for intravesical injection with cocktail.

So, bladder pain syndrome is a complex and poorly understood entity where the conservative measures are universally recommended as first line therapy. One treatment doesn't help every patient and therefore treatment should be targeted and multi model. The perfect cocktail doesn't exist, however this cocktail injections had been under use by Prof. Rane for IC/BPS patients for the last 15 years. However, the main issue is to show that the bladder injections are safe and it's effective for treatment of pain, especially severe pain in patients who present with severe interstitial cystitis and bladder pain syndrome.

Presenter

Prof. Dr. Ajay Rane
Professor, Chair, and Head Department of
Obstetrics & Gynaecology
JAMES COOK UNIVERSITY Consultant Urogynaecologist
The Townsville and Mater HospitalsTownsville, Queensland

The Blog is written by Dr. Sapna Biswas [Scientific Writer - GIBS] while it was presented by me at GIBS 2021 6th Annual Conference on IC/BPS.
- Prof. Dr. Ajay Rane

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

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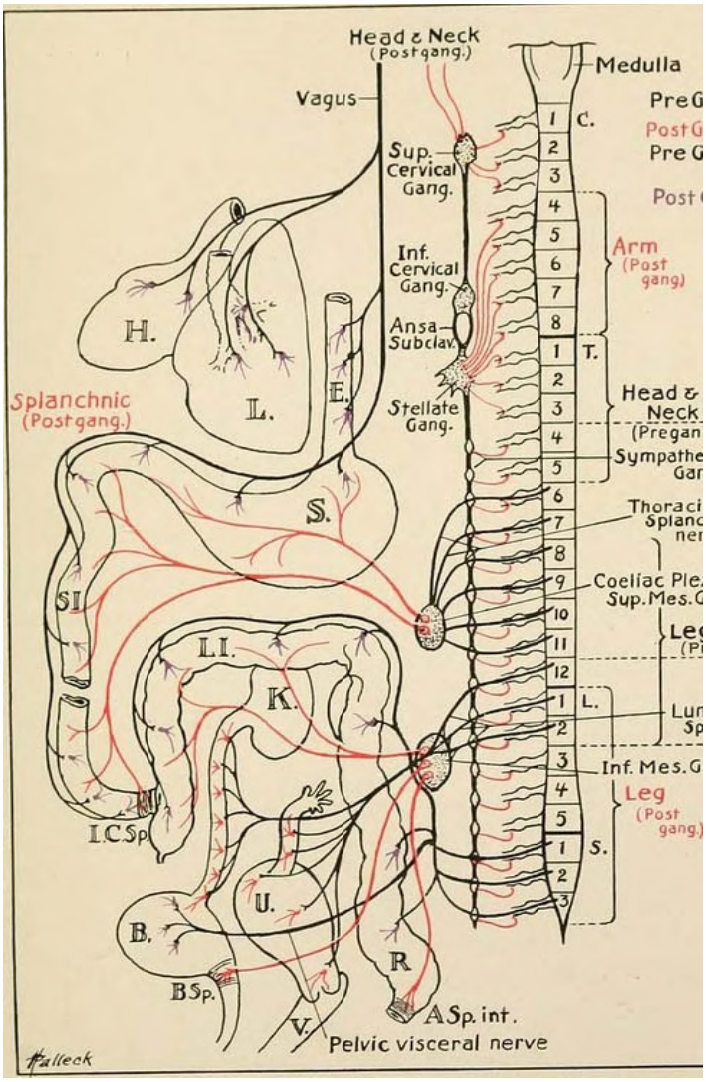
GIBS News Letter

Stimulating Vagus Nerve Through Conservation Approach to Help with Bladder Pain Syndrome, Associated Anxiety and Digestive Symptoms.

Vagus nerve has gained quite the traction from articles in the scientific journals to health magazines, blogs and social media. Although there is limited research, many patients and practitioner swear by its positive effects, so much so that many claim to have their lives changed by vagus nerve stimulation therapies. Vagus nervehas been known as the wandering nerve due to its root at the brainstem and innervating many organs along its path such as pharynx, larynx, heart, lungs and digestive tract from esophagus to recto-colon. Vagus nerve makes up for the most of the parasympathetic nervous system. Vagal nerve stimulation has shown anti-nociceptive effect(3), anti-inflammatory properties through afferent and efferent pathways(1) which can be applied to the IC/BPS patient population.



The above image appreciate the most widely distributed and longest cranial nerve

The Polyvagal Theory

"The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them." William Lawrence Bragg.

The quote applied well to the polyvagal theory. Traditionally, vagus(dorsal) nerve was thought to have only the rest and digest function. Dr. Stephen Porges, introduced the PolyagalTherory in 1994 and looks at autonomic nervous system as 3 different neural circuit, working together to achieve homeostasis, and functional appropriately to meet the environmental and social demands. The ventral branch of the vagus nerve(positive states of relaxation an dsocial engagement), spinal sympathetic chain (fight or flight), the dorsal branch of vagus nerve(slowdown, shutdown and depressive behavior). Polyvagal theory can be the explanation of the mind body connection or the brain-gut connection. Many times we neglect the social, emotional , psychological aspect of the disease when it might be the key to puzzle of chronic pain and anxiety and improving vagal tone can be one of the many tools to help those aspects of the disease. (2)

Vagus Nerve And Pelvic Floor

In a study done by Cahalan et al, 15 patients with mean chronic pelvic pain of 12.3 years underwent RAVANS (respiratory-gated auricular vagal afferent nerve stimulation) compared with NVAS (nonvagal auricular stimulation) as control over 2 sessions, spaced one week apart. RAVANS demonstrated a trend for reduced evoked pain intensity and temporal summation of mechanical pain and significant reduced anxiety compared to NVAS.(3)

With history of chronic pain, many people hold their tension in their pelvic and abdominal muscles which further aggravate their pain. Doing pelvic floor relaxation through either breathing or manual therapy has been shown to improve the vagal tone through regulating the posterior vagus nerve. A lot of pelvic functions are performed when we feel safe (in bedroom , in bathroom ,etc) We have all heard the classic example that when there is fire, we won't think about pooping. But our patients might be living in this sympathetic overdrive state for years!

With IC/BPS, the chronic nature of the disease can have a toll on physical, emotional and social functioning.

Patients can go in to sympathetic overdrive leading to further pain, anxiety, gastrointestinal and other systemic symptoms.

Below are some of the ways to stimulate vagus nerve that can be suggested to the patient that an be incorporated I their daily life.(1,2)

1. Alternate Nostril Breathing
2. Singing
3. Socializing with people you trust and enjoy
4. Movement
5. Meditation
6. Prayer/Chanting
7. Yoga/ Tai chi
8. Chewing you food properly and many others

Exercises To Stimulate Vagus Nerve:

These exercises are based on the book by Dr. Stanley Rosenberg(2). I use it patients who are anxious before start of the session and notice a difference. Although, there is no quantifiable data about the efficacy of these exercises, it has shown mixed results clinically for me and my colleagues.

Exercises To Stimulate Vagus Nerve:

These exercises are based on the book by Dr.Stanley Rosenberg(2). I use it patients who are anxious before start of the session and notice a difference. Although, there is no quantifiable data about the efficacy of these exercises, it has shown mixed results clinically for me and my colleagues.

Basic Exercise: This exercise claims to reposition the atlas(C1) on axis (C2) and improved neck mobility and entire spine and improves blood flow to the brain stem, which can in turn have a positive effect on ventral branch of vagus nerve.

POSITION

It is better to start in lying down and then once you are proficient you can do it in sitting.

STEP 1

Weave the fingers of one hand with the fingers of the other hand.

STEP 2

Put them behind your head putting the weight on your head on your interwoven fingers.

STEP 3

Keeping head in place, look to the right, only with your eyes as far as you can. Hold for 30-60sec and you might feel swallow, sigh or yawn.

STEP 4

Now repeat on left. You might be dizzy after doing this exercise, so take 1-2 min before you stand up and move.

Here's to the vagus nerve and hoping that it provides us with one more tool/perspective to help the complex IC/BPS patients holistically!

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GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

Volume 4 Issue 8 September 2022

GIBS News Letter

Supplement

PILLAR TO POST.... Multiple Clinicians; BEFORE ... A correct DIAGNOSIS... A successful TREATMENT - TIME FOR AN UPDATE

For quite some time now, I have been constantly struggling to find the right title for this newsletter. Continuous brainstorming, more than 15 times of video reviews and reading through different articles did not help me to find a suitable title. And finally, this morning when I was reading through an article on the diagnostic tools for Interstitial Cystitis/ Bladder pain Syndrome, the suitable title hit my imaginations and, I started writing the newsletter.

Dr. Roger R. Dmochowski, Professor Urology, Gynecology and Surgery at Vanderbelt University, Nashville, USA, in his talk during the Global Interstitial Cystitis Bladder Pain Society (GIBS), 2021 meeting have focused on the latest updates in the field of IC/BPS diagnosis, treatment modality, symptoms and many more other important aspects with many more insightful thoughts on IC/BPS. He shared his views on the same, as well as pointing out the dos and don'ts during the conditions of suffering IC/BPS and updated the delegates about where we stand with IC/BPS in the current time frame. Dr. Roger emphasized on the work done by him and Dr. Lindsay Mccarron together as a team for a wonderful ground breaking work in IC/BPS.

As per Dr. Roger, it is still a challenge to understand the diagnosis of IC/BPS, the cause of the condition and, the evaluation of the best management or treatment modality. It is very challenging especially if the patient has fixed pain syndrome. There has been a continuous evolution in the definition of the condition. As per the early data findings from 1990's which were cited by the NIDDK were too restrictive and considered too many exclusion criteria, however the International Continence Society (ICS) tagged it as Painful Bladder

Syndrome (with a focus on the pain condition as the prime criteria) a condition involving suprapubic pain with bladder filling which is considered to be improved by bladder emptying, Urinary symptoms includes urinary frequency and urgency with nocturia which is considered to occur in the absence of an identifiable pathology. It is known that many of the urologic conditions there are overlapping syndromes and conditions that contribute painful bladder syndrome or interstitial cystitis.

One of such condition is Overactive Bladder dry which is a very much common condition, however pelvic pain without urinary dysfunction associated with conditions such as endometriosis or fibromyalgia are also few amongst such overlapping conditions and then IC/BPS which obviously has been known to overlap with the Overactive Bladder Dry Syndrome, and Pelvic pain with no LUTS as well. Such overlapping conditions confuse the diagnosis and misdiagnosis occurs.

Coming to the definition of diagnosis of IC/BPS, the term Painful Bladder Syndrome was considered to be much more directive to the condition. It is predominantly a condition impacting the female population who are in the middle decades of their age. Now a days there has been increasing recognition in childhood voiding dysfunction contribution to the lower urinary tract symptoms. There isa persistence with some of these symptoms into adulthood and therefore, many patients are actually transitional urology patients who had experienced some of the symptoms and continue to experience the same in their adulthood too. It is known that occasional pain syndrome generally occurs after pelvic surgery, especially hysterectomy. It is also known, that with some patients there is a very strong historical relationship with urinary tract infection and many of these patients have constellation of other morphologic conditions such as migraine headache, fibromyalgia and irritable bowel syndrome. Some patients with painful bladder syndrome also exhibit onset of certain things such as reflex sympathetic dystrophy. Around 30% concordance between all of the other syndromes being present and painful bladder syndrome is being noticed. A significant short-term variability is being noted when the natural history of the condition is being evaluated. For many patients the long-term course is best defined in terms that we use for multiple sclerosis, relapsing, remitting. It is known that exacerbations and certain external irritants certainly contribute to the occurrence of the syndrome including history of urinary tract infection or current urinary tract infections, food ingestions, stress a significant contributor to the cause of this syndrome along with menstrual association was also noticed to be a prominent contributor in some of the young women. Dr. Roger considered it to be important to focus upon the goal of the evaluation and as per him the goal has to be reasonable. He feels, in terms of the relationship of the symptoms to the lower urinary tract symptoms. It is important to exclude the excludable conditions such as neurogenic disease, other functional disorders as there are fair chance of clouding the diagnosis. He also mentioned the navailability of definitive diagnosis and many urologists make suppositions based upon confluence of symptoms that constitute the IC/BPS. Hence, definitive diagnosis is a challenge as there is a lack of either an objective criterion that helps in specific diagnosis and generally it is the elements from multiple areas that is being used to make the final diagnosis. Dr. Roger also suggested a large group of differential diagnosis. Carcinoma in situ, is one such condition, which is although a very problematic issue and is very unusual in IC/BPS population. However, it must be considered especially when there is hematuria. There are patients with reflex neurogenic disease from multiple sclerosis that predominantly affect the pelvic organ. Also, prior toxin exposure is one more criterion that must be considered as, most of the reported IC/BPS cases exhibited an associated condition of radiation-induced cystitis from prior treatment of a gynecologic malignancy. Variety of other conditions such as anatomic lesion too must be considered, i.e. urethral diverticulum which are associated with painful voiding and voiding dysfunction capable to mimic IC/BPS.

A clear history – A crucial challenge... What is to be done as a part of Evaluation???

Solutions may be found from a critical history with all the information including the comorbidities and co-presenting conditions, which requires a confluent management with a multi-disciplinary evaluation. Focused physical examination of the Pelvic floor and pelvic region in case of women to determine the reproducibility of pain and palpation of the pelvic musculature, digital rectal examination in cases of male is a must, urinalysis and urine culture must be viewed along with all the guideline documents as being the other critical elements for the absolute components of the diagnostic schema. It is important that the individual knows his condition cannot be cured but care

givers are attempting to improve and ameliorate the condition with various interventions and modulations.

Other measures to be taken...

Symptom indices such as visual analogue scores, are heavily relied upon as it is an important aspect to determine the baseline of the gravity of the symptoms and helpful in the assessment of the progression of the symptoms. The next that may be focused upon is the voiding logs to establish baseline impact in cases where the individuals have significant voiding dysfunction. A way has been found from the primary use of cystoscopy and urodynamics, although there are conditions and circumstances where both of these techniques are applied. Many times, cystoscopy is reserved for the time of anesthetic hydrodistension to help determine morphologic issues in the bladder as well. Symptom scores are not specific, as they do allow quantification of baseline evaluation but also post-therapeutic baseline evaluation. The voiding diary is utilized as a time volume chart. Different arguments on the length of the diary are being noticed, to which the solution was 1-day voiding diary is considered to be the absolute minimum as the patient concordance with 3-day voiding diary was found to be difficult. During this, conditions of polyuria was important to be excluded. The voiding diary maintenance is a method for functional voiding assistance.

How about the role of Cystoscopy and Hydrodistension???

It has been clearly mentioned by Dr. Roger, that these are not the diagnostic tools, but definitely capable to impart therapeutic benefit also helps in occasional visualization of some malicious lesions and some ulcer dependent diseases. As per Dr. Roger, if a hunner ulcer is diagnosed using cystoscopy and hydrodistension, then he may render some benefit by focal therapy to those ulcerogenic lesions by focusing his therapy precisely on those lesions. Though a cystoscopy reveals glomerulations, however glomerulations are not specific to IC/BPS and may be seen associated with other conditions after cystoscopy. Also, cystoscopy revealing hunner positive conditions is a sub-component of IC/BPS. Only about 10 – 20% of the patient demonstrate the hunner ulcers during the course of IC/BPS condition.

There are caveats with cystoscopy and hydrodistension. Anesthetic hydrodistension gives an idea of the daily functional reserve, DE functionalization and helps in recognition of a cadre of elderly women, who possess very small bladder capacity. Such patients often benefited from urinary diversion. The appearance of hunner's ulcer on cystoscopy allows directive local therapy with thermo-therapeutic intervention. Dr. Roger recommends electrocautery may be used in such conditions, however some use laser therapy.

Role of Biopsy in IC/BPS

Biopsy is not recommended in this condition due to poor pathologic correlation with IC/BPS. Also, it is from the evidence of biopsy of some individuals that they have an ischemic or a noxic component to thebladder much as observed in patients with myocardial disease and there has been an increasing role of the potential for hypoxia especially in certain sub-groups including the individuals with bladder DE functionalization with markedly small bladders in the elderly group. It has been thought that may be predominantly or significantly driven by vascular insufficiency at the time of evaluation of the condition.

Different Treatment and Management Modality Ulcers are generally seen in older patients and are a different path of physiology, associated with bladder capacity impact and exhibits increased inflammation on biopsy which is benefited by thermotherapy.

A long-term therapy for the condition must have a flexible algorithm, with individualized treatment modality, unique approach for each individual due to unique presentation of each individual in their condition and the excellent assessment of the patient's symptoms must be performed as the most bothersome concern are critical to underscore a reasonable ongoing treatment algorithm. It has been also seen that the evidence basis for the treatment is improving, however still lacks when level one evidence and the paucity of that is considered.

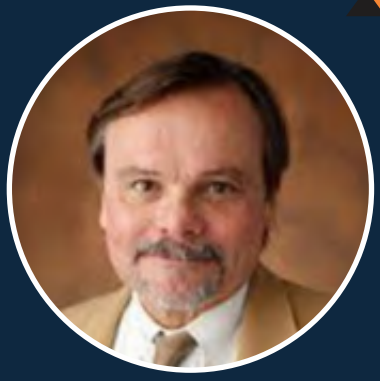
It has been noted that there's no single unified approach but a simple therapeutic regimen to be followed. There are basic principles of the therapy that should be considered. Sequential therapy is often needed in the condition and combination therapy as a corner stone may be utilized. Other therapies include pharmacotherapy, behavioral therapy, cognitive therapy is also important. In conditions of flare, therapy must be planned for directed therapy to improve flare related symptoms. It must also be understood that there is a high degree of emotional overlay with this condition. Often anger and hostility is observed towards the care provider due to the chronicity of the condition and perceived lack of motivation from the patient's end due to prior negative experience from the health care and lack of interest or lack of concern regarding the severity of the condition towards

the patient's syndrome. Also, it is very important to be cognizant of stress exacerbations as management of stress in conditions of IC/BPS is extremely critical in such individuals. The availability of in-clinic supports such as nurse practitioners, physiotherapists who work and interact with patients and such individuals, and behavioral psychologists, play a vital role to help such stressful situations of individuals suffering from the syndrome. Such methods of management are aimed at providing a holistic multidisciplinary approach by providing mental support, physiotherapeutic evaluation, rheumatology in conditions of fibromyalgia, pain management, gynecologic consultation, urologic consultation and gastrointestinal consultation.

Cognitive behavioral intervention is too a very crucial for the management of behavioral aspect of patients suffering from IC/BPS and is very much supported by Dr. Mccarron. Functional disorders are driven by patient's responsiveness and cognitive behavioral intervention was found to be the single aspect that benefit patients with this syndrome to the maximum. Conservative therapy includes restriction of accelerants of symptomatology, following a restricted diet is crucial, bladder retraining and adjunctive therapies are few more such as stress reduction and physical exercise. Dietary considerations must be individualized, as there may be unique irritants for unique individuals.

Complementary therapy has these days become a more focused area of interest in the management of IC/BPS. Mucosal rehabilitants such as chondroitin and glucosamine have gained substantial interest, however sufficient data is unavailable on this. Data regarding Hyaluronic acid is found to be building of its potential benefits in a small number of patients with IC/BPS. Asper Dr. Roger, once the invasive therapies are being considered, hydrodistension may be repeated once on an annual basis, multimodal oral therapy, multimodal intravesical therapy and finally salvage therapy are inclusive of very rare palliative diversion. The development of alternative pharmacotherapies is also noted in the current trend of treatment and management modality. Neuromodulation has gained some importance as it is found to benefit some individuals suffering with the syndrome. Bladder replacement must be rarely considered. There are a variety of immunologic investigational therapies, but one thing is not to be forgotten that those are immunologic investigational therapies with no assured findings as yet. Latest data findings have also focused on Leukotriene Receptor Blockade therapy, Gabapentin has also shown some of the benefits in the conditions of IC/BPS, Systemic steroids have also been reported with some benefits in some individuals, Cyclosporine A remains a consideration for the condition and is also being reported with some benefits and exists in guideline recommendations. Finally sacral nerve stimulation, which is not yet approved for painful bladder syndrome, however may help individuals with urgency, frequency and improve patient quality of life. Sacral nerve stimulation will not help to resolve conditions of pain though, but has been reported to exhibit benefits in individuals and some percutaneous trials.

Hence a lot of effort for improvement in the systematic delivery of intervention has been noticed. With surgical intervention, bladder replacement or augmentation therapy is highly not recommended in the population with this syndrome, as recurrent conditions are developed in the remnant bladder. Hence, with treatment and management modality the future seems to be bright and with lots of developmental hopes associated with treatment and management of painful bladder syndrome.



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The Blog is written by Dr. Sapna Biswas [Scientific Writer - GIBS] while it was presented by me at GIBS 2021 6th Annual Conference on IC/BPS.

- Prof. Dr. Roger Dmochowski

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

Volume 4 Issue 9 October 2022

GIBS News Letter

Supplement

Augment The Treatment of IC/BPS: Intravesical Instillation of PPS - A Boon for Life

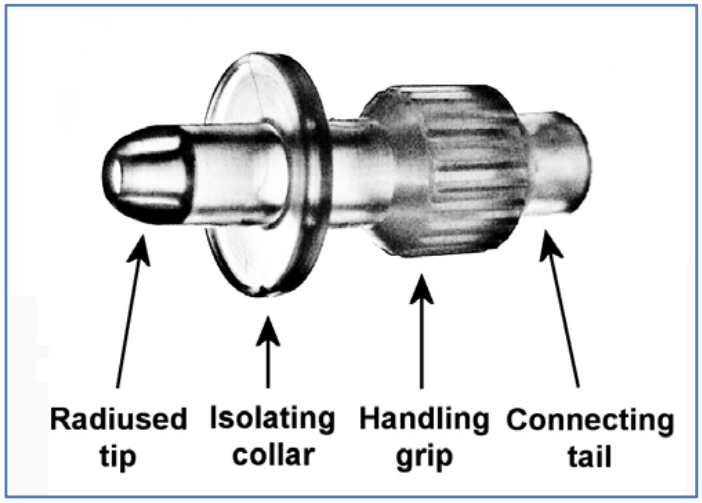
It is already known that Interstitial Cystitis/ Bladder Pain Syndrome is a chronic, non-infectious, inflammatory condition of poorly understood aetiology that affects the urinary bladder.It has anintense impact on the psychological and social wellbeing of the patient if symptoms or urinary urgency, frequency and severe bladder pain are inadequately treated. So far only oral pentosan had been cited in literature to have positive impact on the condition and with no severe side effects, however it is a slow acting drug with lesser bioavailability unlike other available fast acting and instant sources of drugs used for treating IC/BPS with severe side effects.There are many other drugs and therapies in the treatment of IC/BPS.

Dr. Sandor Lovasz Ph.D. (Hungary) emphasized in his talk during Global Interstitial Cystitis Bladder Pain Society (GIBS) Congress held on August 28th, 2021,one such therapy and discussed the new aspects of thetherapy in IC/BPS. He accentuated the impact of intravesical therapy so beautifully, it clearly states the high efficacy of drug with no severe side effects when given intravesical instillation. He had put some lighton why local instillation therapies are used, the advantages of instillation therapies, what are the drugs generally used for such therapies, what kind of medications can be instilled, when and in which frequency it can be recommended to perform. However, scarcely it is spoken about how one may do this instillation, as all conventional bladder instillation is recommended to be performed using a urethral catheterization which makes the therapy extremely painful. Aware of the painful conditions, significant number of patients refuse the instillation procedure, though this is the only mode to get relief faster, as the instillation of the drug is local intravesical. Not only the pain, but also the expensive therapy, the time to visit the doctor every time an instillation needed refrains the patient from

accepting the instillation therapy.Hence, an invention of a catheter-free instillation method by using the syringe adapter which is called “UroDapter” is done to prevent the pain during bladder instillation, to improve patients' quality of life and to convert instillation therapy into a pain-free procedure. It also supports the mases to help deal with the condition smoothly and attain an improved quality of life.

Uro Dapter… How it works?

It seems to be a boon for all those suffering patients. UroDapter is a tiny plastic adapter which fits overboth Luer-lock and Luer-slip syringes.



over the surface of the peri-orifical surface and then the

The main part of the Uro Dapter is the flexible isolatingcollar for a leakage free instillation,which fits instillation may be performed in a leakage-free way. It can be used in both the genders. Simultaneous treatment of the bladder and the urethral mucosa can be done by use of UroDapter which is the greatest advantage of this method. The need of catheterization for the instillation is eliminated and hence there is no mechanical lesion on the urethral mucosa, completely pain-free, quick, and simple procedure. The easy procedure convinces the patient to adopt this method without fear.

UroStill is an assistive device for self-instillation in female patients in combination with the advantages of a syringe adapter. There is a micro video camera which helps targeting the orifice which eases the procedure to have an external view on how the insertion is done and the built-in camera enhances the visualization on how the orifice can be targeted. A clear visualization of the treatment or under-treatment. Due to its many advantages the self-instillation by using the UroStill assistive device should be regarded as the optimal solution of the future. orifice can be performed without catheterization due to the use of syringe adapter. It is completely pain-free, less expensive, and the patient is completely independent of deciding the time and frequency of the treatment at home which helps to prevent over-

Let's Welcome the Arrival of UroDapter for Patientsof IC/BPS. We are here for YOU!

INTRAVESICAL COCKTAILS (RESCUE SOLUTIONS)

1. Anaesthetic cocktail-Robert Moldwin, MD

1:1 mixture of 0.5% Marcaine and 2% Lidocaine jelly – about 40 cc total.
To this solution are added: Heparin sulphate 10,000 IU Triamcinolone 40 mg, Gentamycin 80 mg or a post-procedural prophylactic antibiotic.

2. Marcain with steroid cocktail-Nagendra Mishra, MD

Marcaine 40 ml 0.5 % (sensorcaine)
Heparin sulphate 10,000 IU
Dexamethasone 2 cc
Sodium bicarbonate 20 ml

3. DMSO cocktail-Philip Hanno, MD.

DMSO (Rimso 50) 50 cc
Sodium bicarbonate 44 meq (one ampule)
Kenalog 10 mg
Heparin sulphate 20,000 IU

4. Heparin cocktail-Kristene Whitmore, MD

Heparin 10,000 units/ml-2ml's
Solucortef 125 mg
Gentamicin 80mg/2ml-2ml's
Sodium Bicarbonate 8.4% -50ml's
Marcaine 0.5% -50 ml's

5. Pentosan polysulfate cocktail - Jurjen J. Bade, MD

Pentosan polysulfate sodium 300mg
(=3 ampules each 100mg), Lidocaine 2% 10cc
Sodium bicarbonate 4.2% (but can also be 4.8%)-10cc
To this should be added sufficient NaCl 0.9%
to reach a total volume of 60cc.

6. Heparin cocktail with alkalinized lidocaine-C. Lowell Parsons, MD

Heparin sulphate 40,000 IU
Lidocaine 2% 8 mL
To reach a total fluid volume of 15 mL

7. Two-step cocktail for GAG replenishment – Sandor Lovasz, MD

1st instillation : Lidocain 2% 10ml
Sodium bicarbonate 8.4% 2 mL
Dexamethasone 4mg 1ml
Methylprednisolone 125mg 2ml
2nd instillation:
Heparin sodium 25,000 IU 5ml
Sodium hyaluronate (1,6%) + Sodium chondroitin sulfate (2%) – 10ml
Sodium bicarbonate 8.4% 2 mL

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The Blog is written by Dr. Sapna Biswas [Scientific Writer - GIBS] while it was presented by me at GIBS2021 6th Annual Conference on IC/BPS. - Dr. Sandor Lovasz

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

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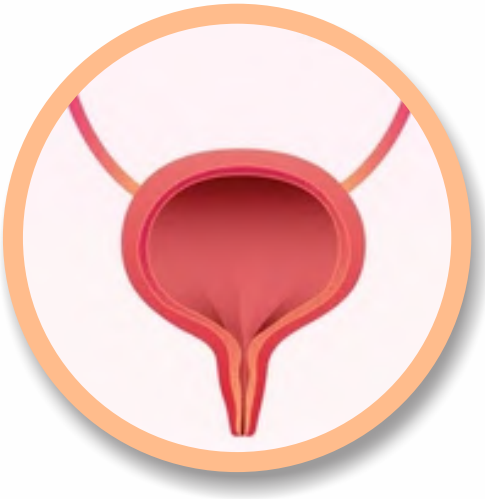
GIBS News Letter

URINARY BIOMARKERS IN IC/BPS



Interstitial cystitis/ Bladder pain syndrome (IC/BPS) is a chronic condition characterised by pain (suprapubic or pelvic) and discomfort related to bladder filling. The symptoms of IC/BPS patientsoften coexist with insomnia, depression, anxiety and sexual dysfunction, thereforeresulting in impaired quality of life and withdrawal from social activities. Notwithstanding the advancement in our understanding of the disease, the exact pathophysiology of this entity is still elusive. Thinking compassionately for the patients who suffer from this illness, I think they are hit by a double whammy: the pain and suffering because of the disease itself and the pain and anxiety caused by the lengthy diagnostic procedures which presently is aimed to rule out other confusable diseases. The entire experience can be overwhelming and devastating for any patient. Hence the search for a simple and reliable diagnostic marker for IC/BPS is an ongoing quest. Today we may be far from attaining one but our quest must go on. Urinary biomarkers are one such diagnostic tools which are garnering a lot of interest from the researchers these days. They are like a ray of hope which presently may seem a distant dream but the days may not be far when they become the mainstream diagnostic tests. With this hope and an eye towards the future let us now understand what are the various urinary biomarkers which may be useful in IC/BPS.

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Biomarker is short for biological marker, and is used as an indication that a biological process in the body has happened or is ongoing. The use of urinary biomarkers to diagnose disease has been a long-standing practice. Ancient clinicians detected glucose in the urine by tasting it or observing whether it attracted ants. The presence of albumin in the urine has been measured as an indicator of renal disease for centuries and in early times could be detected via the so-called "foam test" to determine whether albumin was present in the urine in large amounts. We have come a long way since those times. The basic premise for the development of research on urine for diagnosis of various bladder conditions is that the urine remains in contact with the bladder mucosa and would thereby carry some biomarkers which would point towards a diagnosis. And moreover, urine is a sample which can easily be collected without any needle prick and hence allows for easy multiple sampling. It has also been seen that urine as a sample has greater stability over serum or blood. These characteristics make urine a promising sample for these kinds of futuristic researches. For IC/BPS, urinary biomarkers are being developed to facilitate its diagnosis (including the differentiation between Hunner Lesion type of IC/BPS (HIC) and non Hunner lesion type (NHIC)) and objective follow-up.

Proteomic biomarkers: Proteomic profiling of the urine revealed several cytokines and chemokines which were associated with IC/BPS and could possibly serve as useful tools to assess treatment outcomes. Proper function of the urothelium requires normal epithelial integrity, which relieson intercellular adhesion molecules and a layer of molecular components on theapical surface of the urothelium, which is composed of GAG. Abnormal expressionsof urothelial-associated proteins, including zonula occludens type 1 (ZO-1), E-cadherin,uroplakin, chondroitin sulfate, and receptors/ion channels have been noted in IC/BPSbladders on bladder biopsy specimens. Uroplakins (UPK) are a family of integralmembrane proteins of bladder urothelium. Overexpression of uroplakin III has also beenshown in bladder of NHIC/BPS. In an animal model of experimental autoimmunecystitis, injection of UPK3A has been shown to induce T-cell attack on the bladder epithelium,resulting in chronic suprapubic hypersensitivity and other symptoms that mimichuman IC/PBS disease. These abnormal alterations may help disrupt urethral barrierand sensory functions, leading to increased afferent nerve activity and manifesting bladdersymptoms such as hypersensitivity, pain, or urgency. Increased levels of UPK3A has been found in urine samples and being investigated as a potential biomarker for IC/BPS.

Erickson et al.[1] and Sakthivel et al.[2] found that several proinflammatorymediators, such as interleukin-6 (IL-6) and CXC chemokines, were increased in both urinaryand serum samples of IC/BPS patients.

Magalhaes et al[3] had published an excellent review on the subject in 2019 and had described these biomarkers. The urinary biomarkers discussedin the study included macrophage inhibitory factor (MIF), nerve growth factor (NGF), methylhistamine, histamine, IL-6, antiproliferative factor (APF), epithelial growth factor (EGF), heparin-binding (HB)- EGF and glycoprotein G5P1. Urinary MIF was studied by Vera et al.4and they verified that urinary MIF was significantly higher in IC/BPS patients with Hunner lesion compared with patients without Hunner lesions and with controls. Patients with lower urinary tract diseases, including stones, tumors,acute bacterial infection, IC/BPS and bladder outlet obstruction,have been found to have increased NGF levels in the urine, serum, and/or bladder tissue. In thebladder, NGF is expressed in the urothelium, smooth muscle, afferent nerves, and ganglia. NGF acts as a chemical mediator in C-fibre afferents that may regulate urinarybladder function. Current findings suggested that the urinary NGF level can bemonitored as a biomarker for IC/PBS severity and for treatment response. In a transgenicmouse model, NGF overexpression in the bladder led to neuronal hypersensitivity andchanged in urinary bladder function. In samples of patients with IC/BPS, increasedlevels of NGF have been noted in the urine and bladder tissue. TheNGF level of serum and urinary in IC/BPS patients was elevated, while the level was alsonot related to the severity of IC/BPS. The urinary NGF level has been shown to beclosely related to the visual analogue scale (VAS) score for inflammatory pain and treatmentoutcome for IC/BPS. Clinical and experimental data in IC/BPS have indicated correlationbetween increased levels of NGF in the bladder tissue and urine and painful inflammatory conditions. These findings suggested that NGF is associated with bladder function, andelevated urinary NGF levels reflect that chronic inflammation occurs in the urinary bladderof IC/BPS patients. NGF might be developed as an indicator for treatment, in order to be asensitive molecular diagnostic tool for IC/BPS[5].

Also, assessing both urine and bladder biopsy samples, Corcoran et al.[6] determined the profile of 23 chemokines in 10 patients with BPS and 10 asymptomatic controls. In urine, univariate analysis showed no significant differences in any of the proteins assessed, but multivariate analysis revealed that

VCAM-1 and ICAM-1 were responsible for the discrimination of urine of IC/BPS patients from that of controls. Lamale et al.[7] investigated urinary histamine, IL-6, and methylhistamine in IC/BPS patients and controls. They found that urinary concentrations of histamine and IL-6 were increased in IC/BPS patients. However, methylhistamine levels had no significant differences between IC/BPS patients and controls. Further logistic regression analysis demonstrated that the best predictor for IC/BPS was a combined model with IL-6 and methylhistamine. According to this model, BPS diagnosis could be established in the following scenarios: lL-6 levels above 2.28 pg/mL regardless of methyl-histamine levels; methylhistamine concentration above 288 pg/mL regardless of IL-6 levels; or IL-6 below 2.28 pg/mL, but methylhistamine levels equal to or higher than 126.56 pg/mL multiplied by the difference between 2.28 and IL-6 levels. This model showed 70% sensitivity, 72.4% specificity, 77.8% positive predictive value, and 63.6% negative predictive value.

Both OAB and IC/BPS might share acommon pathway, for example, mast cell infiltration was found in both diseases. However,abnormal urothelial barrier function only occurred in IC/BPS patients, but not in those withOAB. Urine CXCL-10 is elevated in patients with IC/BPS, but not in OAB patients[8]. The upregulated levels of serum TNF- α, IL-1, 6, and 8, and urine CXCL-10 level in IC/BPSpatients might help provide as an appropriate diagnostic tool. The increased expression ofproinflammatory cytokines and chemokine levels in the serum of IC/BPS patients indicatedthat not only the activation of mast cell, but also inflammatory mediators might play keyroles in the pathogenesis of IC/BPS. Serum CRP is elevated in patients with LUTSand IC/BPS. The CRP levels ofserum and urine might serve as a biomarker of local bladder inflammation to distinguishpatients with IC/BPS.

Keay et al.[9] found that APF was increased in IC/BPS patients compared to controls, but HB-EGF concentrations were decreased in IC/BPS patients. APF glycoprotein is secreted by bladder urothelial cells from IC/BPS patients and slows down the growth of urothelial cells. APF may mediate the pathological changes observed in IC/BPS, including inhibition of cell growth, increased barrier permeability and reduced proteins expression (e.g., cadherins), while promoting the formation of intercellular complexes. Increased susceptibility to urothelial damage may bedue to altered factors that regulate the development of structural elements. Therefore, the seproteases have been proposed as potential biomarkers or to provide assessment of disease progression but have not been validated in lower urinary tract disorders. An increased APF and lower expression of IL-8 have been found in IC/BPS bladders, which may contributeto IC/BPS pathophysiology. Furuta et al[10] suggested that increased levels of VEGF in urine may signal increased angiogenesis in the bladder which in turn is suggestive of VEGF induced bladder fibrosis, and reduced bladder capacity after chronic inflammation. This VEGF is also being explored as a potential biomarker for the prognosis and as a marker for assessing treatment outcomes.

ATP is released from urothelium in response to bladder stretch and could act onurothelial purinergic receptors. Patients with IC/BPS have increased afferent nerve densityand ATP release, which might affect the symptoms of pain, urgency and frequency. Studies also suggest that ATP release may influence function of myofibroblasts and afferent nerveendings. In patients with IC/BPS, urinary ATP levels were significantly higher than control. Blocking ATP release improved the symptoms of pain, urgency, and frequency for IC/BPS patients. Similar to the data in human IC/BPS, a significant increasein stretch-evoked ATP release in IC/BPS feline model and in CYP-induced rats caused chronic bladder inflammation.

Not all biomarkers are increased in patients with IC/BPS. The pathophysiology of IC/BPS urothelium is involved in an aberrant synthesis of bacterial defence molecules such as GP51 and Byrne et al.[11] demonstrated that the level of urinary glycoproteinGP51 secreted from urothelial cells was reduced in IC/BPS patients.

Lee and co-workers[12] investigated ß-defensin 2, which is an antimicrobial peptide normally expressed in the bladder upon inflammation and persistently expressed in IC/BPS. In their study, the authors compared the urine BD-2 levels in three female groups, normal controls, non-Hunner-type IC (NHIC) and Hunner-type IC (HIC). They found significant higher BD-2 levels in the HIC group than in the control or NHIC. Those expression levels correlated with higher mast cell counts in HIC. These finding further support our understanding of HIC as a chronic inflammation condition, possibly altering the bladder microbiota.

Metabolomic Biomarkers: At present, urinary metabolomic biomarker studies are primarily conducted either by Nuclear magnetic resonance (NMR) spectroscopy or liquid chromatography mass spectrometry (LQ-MS)-based identification. Using liquid chromatography-MS in urine samples of 40 women with BPS and 40 controls, principal component analysis by Parker et al.[13] demonstrated there to be two distinctmetabolomic profiles in women with BPS.The

first(G1) had a profile similar to controls, which was distinct fromthe metabolomic profile of the second (G2). To determineexactly which metabolites and classes of metabolites coulddistinguish patients in subgroup G2 from the others, the authors used graphic representations and found six metabolitesmost closely associated with IC/BPS. One of them was a molecule highly abundant in G2 samples, found at a chromatographic peak of 369 m/z, which corresponded to Etio-S.Analysis of variance comparing Etio-S levels in the twoBPS subgroups and controls showed that the correlation reported was statistically significant; and a validation study determined that elevated Etio-S is a good predictor of IC/BPS, with91.2% sensibility, 87.4% specificity, and 0.92 AUC. In thelongitudinal analysis of women in this cohort, differences inEtio-S persisted, showing that these changes are long-lasting.

DNA methylation biomarkers for IC: In their research Magalhaes et al. foundthat DNA methylation in urine samples was associated withIC/BPS. Bradley et al[14] determined DNA methylationprofiles in IC/BPS and controls. They found thatthere was no genome-scale significantly different methylationin CpG sites. Among the methylated CpG sites, the mostprominent enrichment pathway was the mitogen-activatedprotein kinase (MAPK) pathway. This pathway had 86% ofsites with hypomethylation in IC/BPS patients compared tothe controls.There is evidence that DNA methylation biomarkersare more sensitive than cytology although there were biomarkerstested on cohorts that varied between studies. A highly selectiv panel of methylation biomarkers may increase the sensitivity and specificity of urine analysis in the clinical studies[15].

Clinical observations imply that IC/BPS develops over a long time and that thesymptoms in early stages are mostly misdiagnosed as related urinary tract diseases. Biomarkers able to discriminate between confusable diseases and IC/BPS at early stages would be of great value for early onsetof specific treatment. Despite our steadily increasing knowledge on the molecular and cellular mechanisms involved in the pathophysiology of IC/BPS, we are still far from understanding this disease. The great spectrum of IC/BPS biomarkers currently under evaluation raises hope that we can develop panels of biomarkers for early detection, stratification, and treatment assessment in future.

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GIBS 2022 Activities

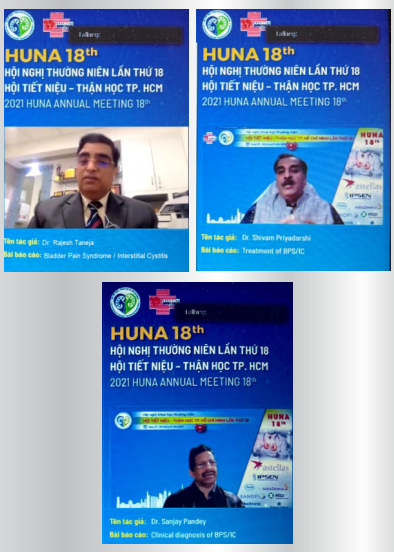
January
8th
2022

18th HUNA [Ho Chi Minh City Association of Urology-Nephrology]
Presents
GIBS-HUNA Symposium on IC/BPS

Theme:

Everything about Bladder on Fire

Time:
13:35-15:05 Vietnamese Time/12:00-13:30 IST



February
27th
2022

Gwalior Obs & Gyn Society [GOGS]

Theme:

Lower Urinary Tract Disorder

TIME:
4:00pm-6:00pm IST

Participant: **120 Plus**

March
6th
2022

GIBS 2nd International IC/BPS Patient Day
GIBS celebrated its 2nd - International IC/BPS Patient Day

TIME:
04:00PM-05:00PM

March
10th
2022

AICC RCOG NZ & NARCHI

Theme:

Pelvic Pain : Is It Interstitial Cystitis/ Bladder Pain Syndrome?

TIME:
4:30PM - 6:30PM IST

Participant: **120 Plus**

GIBS 2022 Activities

Female Pelvic Pain Association & Chennai Menopause Society

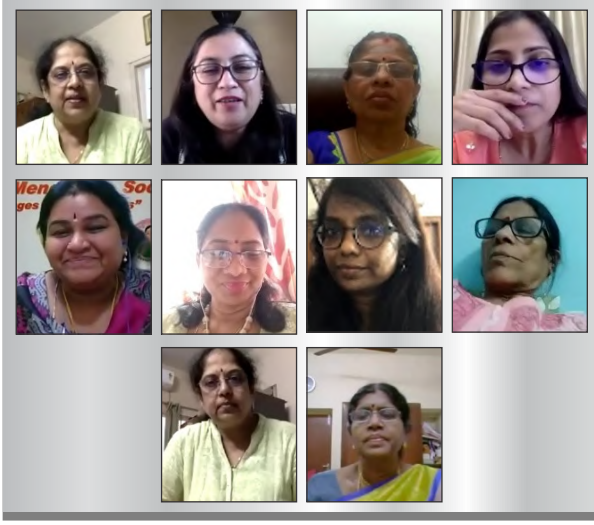
March 26th 2022

Theme:

Midlife & Bladder

TIME:
4:30PM - 6:30PM IST

Participant: **120 Plus**



Obstetrics & Gynaecology Forum of Sonipath

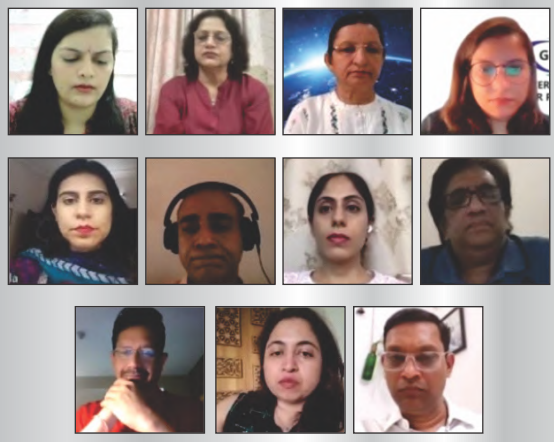
March 30th 2022

Theme:

Diving into Bladder Pain Conundrum in Women

TIME:
3:30pm-5:30pm IST

Participant: **120 Plus**



Baroda Obs & Gyn Society [BOGS]

April 22nd 2022

Theme:

Interstitial Cystitis- Is It your Domain?

TIME:
3:30pm-5:30pm IST

Participant: **120 Plus**

LUDHIANA OBSTETRICS & GYNECOLOGICAL SOCIETY

July 1ST 2022

THEME

Demystifying Chronic Pelvic Pain - Is It Uterus/ Ovaries/ Bladder Pain

TIME
8:00PM-9:30PM IST

GLOBAL INTERSTITIAL CYSTITIS, BLADDER PAIN SOCIETY

EDUCATE, IDENTIFY, TREAT

Fighting the Fire in Bladder

GIBS 2022

7th Annual Congress on IC/BPS

27th & 28th August 2022

'Save a Bladder - Save a Family'

It is immense pleasure to state that GIBS 2022 is a grand success through offline & online with its "Theme: Save a Bladder - Save a Family"

The aim of the GIBS is to disseminate the knowledge of IC to spread awareness about the science behind it. A short video on GIBS milestones was discussed. All these years, it took us great hard work and dedication to reach the place where we are today. As it is rightly said, "Nothing comes easy; it takes dedication and hard work".

This year's meeting received over 350 zoom registrations from all over the globe, making it as 281 participants on Day 1 and 286 participants on Day 2.

And we had 120 plus participants for physical conference, involving our Foreign Delegates from Bangladesh, Russia, Hungary, & Nepal.

The journey has taken a tremendous peak! GIBS is determined to disseminate the evolving science of IC/BPS in all the seven continents, hopefully by the end of next year, in order to reach out to all those patients suffering from this disease and their physicians.

The planning for the further GIBS events & the 8th GIBS (2023) Annual congress has already started coining the Theme: Compassion and Care for Bladder Flare which will be held on 26th & 27th August 2023

Information about the other details would follow through emails, as the program evolves through the various planning stages.

Looking forward to another exciting year full of educational activities on the subject of IC/ BPS.

GIBS 2022 Activities

GIBS Session in Annual conference of the Russia Neurourology Society

Moscow GIBS

30-31 October 2022

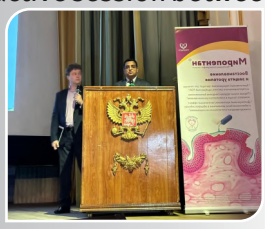
On 30 October, there was a round table involving 25 urologists from Russia. The session continued for more than three and a half hours without break, despite it was offered to delegates and was turned down.

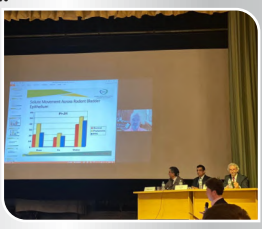
The deliberations included the introduction of the subject of IC/BPS, etiopathogenesis, anatomy, hysiology, and pathology of GAG layer followed by the clinical use of Oral PPS to replenish GAG layer with attendant controversies.

On 31 October 2022, a session of two hours was held on during the Annual conference of the Russian Neurourology Society.

Almost 100 delegates, all of them urologists were part of this session. The session included

1. Talk by Dr Rajesh Taneja focussed on the Management of IC/ BPS.
2. Online lecture by Dr Lowel C Parsons as a GIBS faculty from California on the basic science behind the pathophysiology of IC/BPS.
3. Lecture by Prof Gevorge Kasyan from Moscow, on the use of Oral PPS in IC BPS.
   This was followed by an interactive session between the audience and the panel.

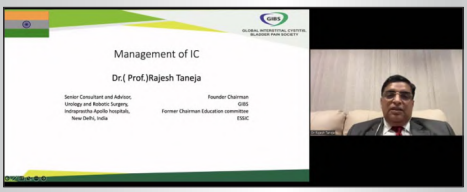


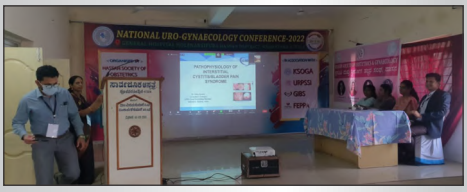
GIBS & FEPPA

Karnataka Joint Session in National Urogynecology Conference [HYBRID]

3rd December 2022

TIME: 12:00 PM – 1:00PM IST



GIBS 2022 Activities

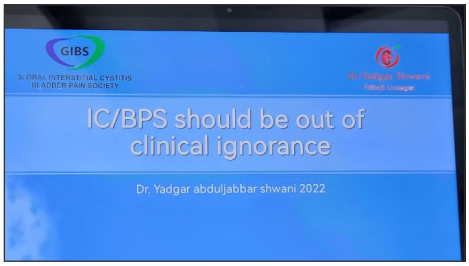
Representation of GIBS in KUA (Kurdistan Urological Association)

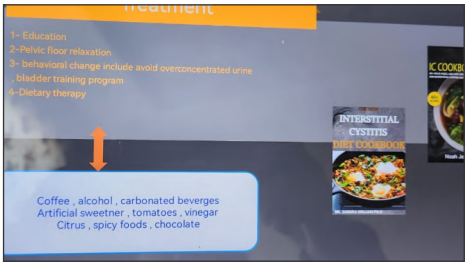
We are happy to share that Dr. Yadgar Shwani, GIBS Global Stalwart has represented GIBS in the 2nd international conferences of Kurdistan Urological Association (KUA) Regional association in Kurdistan region in north of Iraq, held on 9th-11th November 2022 in Divan hotel in Erbil city capital of Kurdistan federal region in Iraq.

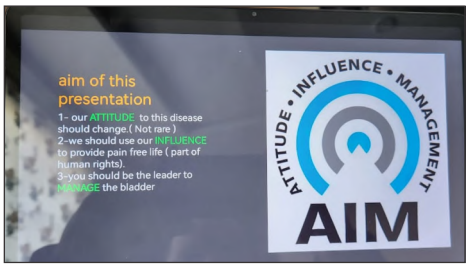
He presented a lecture on Interstitial cystitis / bladder pain syndrome that should be out of clinical ignorance to save the bladder because it is the responsibility of the urologist, fortunately it was a very fruitful presentation with more than 200 attendees.

GIBS appreciate his endeavor in spreading the knowledge on the subject IC/BPS.

Looking forward for more this kind of initiation from our Stalwarts.







GIBS

Upcoming Activities

GIBS
USICON Session
[Gurugram, Haryana]

02 February 2023

Theme

Compassion and Care for Bladder Flare

3rd GIBS
International PATIENT DAY *Celebration*

5th March 2023

GIBS
8th Annual Congress on IC/BPS

26th & 27th August 2023

Theme

Compassion and Care for Bladder Flare

Stay Tuned

to our website for more information:
https://gibsociety.com/

Join Us! Become a Member of GIBS
(https://gibsociety.com/become-a-lifetime-member/)

Call for GIBS Newsletter

Be the
NEXT Author!

GIBS 2023

Registration Will
Open Soon

FOR ANY ASSISTANCE CONTACT

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