

The Chinese approach to complementary and alternative medicine treatment for interstitial cystitis/bladder pain syndrome

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Abstract: Management of interstitial cystitis/bladder pain syndrome (IC/BPS) remains a challenge due to poor understanding on its etiology. Complementary and alternative medicine (CAM), as an optional treatment, has been widely used, because no definitive conventional therapy is available. The different domain of CAM provides miscellaneous treatments for IC/BPS, which mainly include dietary modification, nutraceuticals, bladder training, biofeedback, yoga, massage, physical therapy, Qigong, traditional Chinese medicine and acupuncture. Clinical evidence has shown that each therapy can certainly benefit a portion of IC/BPS patients. However, the target patient group of each therapy has not been well studied and randomized, controlled trials are needed to further confirm the efficacy and reliability of CAM on managing IC/BPS. Despite these limitations, CAM therapeutic characteristics including non-invasive and effectiveness for specific patients allow clinicians and patients to realize multimodal and individualized therapy for IC/BPS.

Keywords: Interstitial cystitis; bladder pain syndrome; complementary and alternative medicine (CAM); integrative medicine; multimodal therapy; individualized therapy

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Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined as suprapubic pain related to bladder filling accompanied by other symptoms such as increased day-time and night-time frequency in the absence of proven urinary tract infection or other obvious pathology. Management of IC/BPS remains a challenge due to the poor understanding of its etiology. Although more than 180 therapies have been used for IC/BPS, none of them is totally effective in all patients (1). Because no definitive therapies are available for IC/BPS (2), many patients resort to complementary and alternative medicine (CAM) therapies. A recent survey based on 1,982 IC/BPS patients revealed that 84.2% had tried CAM and 55% were recommended to use CAM by their physicians (3). This clearly indicates that CAM is widely

accepted by both patients and clinicians. Unfortunately, only limited evidence exists for the CAM therapy of IC/BPS.

CAM refers to a series of medical and health care practices and products that are not considered to be part of conventional medicine (4). The National Center for Complementary and Alternative Medicine at the NIH has grouped CAM into five domains: (I) biologically-based therapies, such as special diets, nutraceuticals and herbal supplement; (II) mind-body interventions, such as meditation, yoga and biofeedback; (III) manipulative and body-based approaches, such as massage and physical therapy; (IV) energy therapies, such as Qigong, Reiki and bioelectromagnetic-based therapies; (V) whole medical systems, such as traditional Chinese medicine, acupuncture and naturopathy (5). Differing from the conventional

treatment, CAM usually focuses on the individual's specific need (6). Moreover, CAM is not restricted as mainstream medical therapies and most of them are over-the-counter medicines, which allow patients to use several CAM therapies simultaneously. These characteristics make CAM studies difficult to provide high quality evidence (7).

Biologically-based therapies

Dietary modifications

It has been widely reported that some foods and beverages exacerbate IC/BPS symptoms. Dietary modifications have been recommended as first-line treatment of IC/BPS in American Urological Association (AUA) guideline (8).

A case-control study, Events Preceding Interstitial Cystitis, revealed that 85% of patients with IC/BPS experienced an aggravation of symptoms after intake of certain foods or beverages (9). The comparison with secondary analysis of the Interstitial Cystitis Database cohort was also involved in that study, which presented a similar proportion (77%) of IC/BPS patients with food sensitivity (9). Furthermore, an internet-based survey found that 95.8% of 598 patients reported an relationship between diet and exacerbated IC/BPS symptoms (10). In terms of specific diet, Koziol *et al.* (11) reported that coffee, tea, spicy food, alcoholic and carbonated beverages consumption affected 52.7% of 374 patients. Gillespie (12) reported that foods high in arylalkylamines, including beer, chocolate, cranberries, mayonnaise, aspartame, nuts, onions, raisins, pineapple, sour cream, wine and yogurt, could trigger the IC/BPS symptoms. Shorter *et al.* (13) evaluated the effect of 175 items on IC/BPS symptoms using a validated questionnaire, which confirmed 35 most problematic comestibles. The worst items were coffee, tea, soda, alcoholic beverages, certain fruits and fruit juices, tomatoes and tomato products, hot peppers, spicy foods and certain artificial sweeteners (13).

To determine the specific time that diet affects IC/BPS symptoms, a study based on 3-day food and voiding dairies showed that symptoms might be worsen within 2 to 4 hours following an intake of irritating food (14). A recent survey, however, showed that time to aggravation of symptoms after ingestion varies from person to person (15). Some patients experienced flares just within a few minutes while others did not notice the symptoms until the next day.

The mechanism of IC/BPS symptoms being triggered by foods and beverages remains unclear. Some hypotheses

have been proposed to explain the relationship between diet and IC/BPS symptoms. An abnormal urothelial barrier due to defective bladder glycosaminoglycan (GAG) layers plays an important role in IC/BPS (16-18). An early hypothesis was that low urine pH induced by diet can irritate the bladder resulting in IC/BPS symptoms. This hypothesis was supported findings that ingestion of acidic foods may exacerbate bladder pain (11,19). However, Fisher *et al.* (20) found no correlation between consumption of acidic foods and decreased urine pH. A prospective, randomized, double-blinded study further showed that the change of urine pH has little effect on IC/BPS symptoms (21). Based on these findings, an alternative theory postulated that bladder epithelial dysfunction allows normal dietary metabolites in urine to become noxious irritants, which generate IC/BPS symptoms (22). Another possible mechanism is "organ cross-talk" theory that flare can be transferred from one organ to another via neural pathways (23). A systematic review showed that bladder and bowel dysfunction may influence one another (24), which may explain the relationship between diet and IC/BPS symptoms.

Despite lack of understanding on exact mechanisms, a dietary changes strategy is considered as the initial treatment for patients with IC/BPS. A study showed that 87.6% of patients reported an improvement after taking up an elimination diet (3). Owing to no standard dietary changes strategy available for all the patients, individualized modifications strategy should be taken into consideration. The basic principle is to eliminate the foods and beverages which may trigger IC/BPS symptoms. On the other hand, it is also required to avoid eliminating unnecessary comestibles, which can ensure patients get enough nutrition from daily foods. A dietary changes strategy asks patients to eliminate all potential sensitive foods and fluids for 2-3 months and then add them stepwise to determine appropriate diet (14). Some experts recommend patients to record their symptoms with regular diet and then put them on the comestibles indentified as least bothersome for 2 weeks. If they don't experience the exacerbated symptoms, the possible sensitive foods and beverages consequently are added one by one with a 3 days waiting period to establish the final dietary strategy (22). *Table 1* lists the foods and beverages with effect on IC/BPS symptoms.

Nutraceuticals

Nutraceuticals are the products isolated from food, plant

Table 1 Foods and beverages related to IC/BPS symptoms

Most bothersome	Least bothersome
Beverages	
Coffee (caffeinated and decaffeinated)	Water
Tea (caffeinated)	Milk (whole and low-fat)
Carbonated beverages (cola, non-cola, diet, and caffeine-free)	Grain drinks
Alcoholic drinks (liquor, beer, wine and champagne)	
Fruits	
Grapefruit (fruit and juice)	Avocado
Orange (fruit and juice)	Blueberries
Pineapple (fruit and juice)	Honeydew melon
Cranberry juice	Pears
Lemon	Raisins
	Watermelon
Vegetables	
Tomato and tomato products	Asparagus
Hot peppers	Broccoli and cauliflower
Onions	Brussels sprouts
	Cabbage
	Carrots
	Celery
	Cucumber
	Mushrooms
	Peas
	Potatoes (white and sweet)
	Radishes
	Squash
	Spinach
	Zucchini
	Yams
Other foods	
Chili	Chicken
Horseradish	Eggs
Vinegar	Turkey
Monosodium glutamate	Beef
Artificial sweeteners	Pork
Saccharin	Lamb
Nuts	Sea foods (shrimp, salmon, and tuna fish)
Spicy foods	Oat
Thai food	Rice
Indian food	Pretzels
Mexican food	Popcorn

Data from Friedlander *et al.* (22), Gordon *et al.* (25) and Gillespie (12). IC/BPS, interstitial cystitis/bladder pain syndrome.

and herb, which can improve health and prevent chronic diseases (26). Some nutraceuticals has been used to relieve IC/BPS symptoms.

L-Arginine

L-arginine is a semi-essential amino acid, which can be converted to nitric oxide (NO) by NO synthase related enzymes. NO is an important regulator for multiple physiological functions of humans. A systematic review revealed that NO pathway plays a major role in regulating lower urinary tract function. Not only can NO modulate bladder afferent neurons activity, but relax the urethral smooth muscle cells (27). Koskela *et al.* (28) found that IC/BPS patients had a significant higher NO formation and up-regulated expression in inducible NO synthase mRNA compared to controls. It is reported that intensive L-arginine supplement may affect NO production and activity (29). Smith *et al.* showed that 6-month oral L-arginine (1,500 mg/day) might relieve IC/BPS patients' pain and urinary symptoms (30) and increase the metabolites of NO synstrate in urine (31). On the contrary, a randomized, double-blind, controlled trial showed that IC/BPS patients did not get clinical significant improvement from L-arginine supplement (32). Another randomized, double-blind, controlled study demonstrated that oral L-arginine can significantly improve IC/BPS symptoms based on per protocol analysis. However, intent-to-treat analysis did not show any notable difference between L-arginine and placebo group (33). Because most of these studies had small sample sizes, the reported outcomes become controversial and the efficacy of L-arginine and effect of NO on IC/BPS still deserve further study.

Quercetin

Quercetin is presented in a number of fruits and vegetables, such as apple, onion, celery and chill pepper. Its antioxidant, anti-inflammatory and immunoregulatory properties have been widely reported by molecular biological and animal studies (34). Some studies have also confirmed its safety for long-term consumption (35,36), which allows use for chronic diseases, such as IC/BPS. Katske *et al.* (37) treated 22 IC/BPS patients with quercetin 500 mg twice a day. Of those, 20 patients completed the 4-week treatment. They reported significant improvement in the O'Leary-Sant Interstitial Cystitis Symptom and Problem Indices (ICSI and ICPI), which decreased from 11.3 ± 0.6 to 5.1 ± 0.7 and from 11.9 ± 0.9 to 4.5 ± 0.5 respectively, and the global assessment score (range from 0-10) (8.2 ± 0.4 vs.

3.5 ± 0.4) after the treatment. In an open-label study (38), 37 female patients with refractory IC/BPS were treated by CystoProtek, which contains quercetin (900 mg/day) and multiple natural GAG components, for 6 months. Most patients experienced a significant decrease in ICSI and ICPI, so did a 52.2% improvement in global assessment score. Three years later, the same authors (39) further reported the efficacy of CystoProtek on refractory IC/BPS based on 252 patients. After 11.2-12.5 months of average treatment period, female and male patients presented a 48.8% and 51.8% reduction in visual analogue scale (range from 1-10) respectively. Furthermore, the study found that patients with severe symptoms got a more significant improvement than the counterparts with mild or moderate symptoms. These studies suggest that quercetin alone or combined with other therapy might be a treatment option for IC/BPS, especially for refractory IC/BPS. However, a prospective, randomized, placebo-controlled trail is needed to provide strong evidence for the efficacy of quercetin.

Probiotics

Probiotics refers to microbial products which when administered in an appropriate amount beneficially affect the host by improving the intestinal microbial balance (40). A systematic review has confirmed its efficacy for irritable bowel syndrome (IBS) (41). It may be a treatment option for IC/BPS patients with comorbid IBS according to "organ cross-talk" theory (25). A survey showed that 58.8% of 442 IC/BPS patients receiving probiotics reported a marked improvement based on a self-evaluation (3). Mansour *et al.* (42) treated two patients with IC/BPS and recurrent urinary tract infection using probiotics combined with L-arginine and cranberry tablets. Following several weeks to 1 year treatment, the two patients reported an 80-100% improvement on their IC/BPS symptoms. The therapeutic mechanism remains unclear and the efficacy of probiotics is needed to be further examined by well-designed clinical trials.

Herbal therapy

Herbal therapy has been used for many urological diseases over the past decades and the effectiveness has been confirmed (43). However, the use of herbal medicine for IC/BPS remains controversial because the efficacy is variable. Some patients report significant improvement, while others experience a worsening of symptoms. Although some animal experiments have demonstrated a remarkable benefit of herbal therapy on IC/BPS, only a few clinical

studies are available. In a pilot study, 25 IC/BPS patients were treated with herbal tea, which is composed of Cornus, Gardenia, Curculigo, Rhubarb, Psoralea, and Rehmannia, twice a day for 6 days a week. An 83% overall response rate was achieved after 3-month treatment (14). In a randomized, controlled study, 56 IC/BPS patients were allocated to receiving intravesical instillation of *Coptis chinensis* extract or nitrofurazone once a week for 3 months. At the end of this period, patients in *Coptis chinensis* extract group presented a significant improvement in pain, frequency and nocturia, but ones in nitrofurazone group did not (44). Due to the varied response to herbal therapy in different individuals, further study needs to focus on finding an herbal formula suitable for the majority of IC/BPS patients. On the other hand, it is also important to identify the specific effect of herbal supplement in different IC/BPS patients, which allow clinicians to realize the individualized herbal therapy.

Other nutrition supplement

Some other nutraceuticals including calcium glycerophosphate (45) and aloe vera extract (14) were reported to be helpful for some cases. However, due to lack of efficacy supported by substantial clinical evidence, these nutrition supplements are not used widely in clinical practice.

Mind-body interventions

Bladder training

Bladder training is a self-control technique suppressing urge to urinate, which has been listed as the first-line treatment in AUA guideline (8). Parsons and Koprowski (46) managed 21 IC/BPS patients using this technique and 71% of them reported at least 50% symptoms relief. Chaiken *et al.* (47) treated 42 refractory IC/BPS patients using bladder training combined with dietary modification and pelvic floor muscle exercises. After 12 weeks treatment, the mean voiding interval was prolonged 93 minutes and 88% of patients claimed a significant symptoms improvement. A randomized, controlled trial showed that combination therapy with bladder training and hydrodistention can increase patients' bladder capacity and reduce frequency more significantly than hydrodistention alone. During 24 weeks follow-up, a lower proportion of patients experienced recurrent bladder pain in combination therapy group compared to hydrodistention group (14.3% *vs.* 34.8%) (48). Although bladder training is easy to practice and has a certain effect, patients may experience greater

discomfort during therapy. To ensure patients can accept the therapy, they should be sufficiently educated prior to bladder training.

Biofeedback

Biofeedback, as a technique enhancing the effect of pelvic floor muscle exercises, has been used to treat various urological diseases, such as stress urinary incontinence and overactive bladder. Its efficacy has also been confirmed by a number of studies. However, the role of biofeedback in managing IC/BPS symptoms is debatable. It has been revealed that pelvic floor muscle over-activity is an important factor contributing to IC/BPS symptoms (49). Biofeedback may relieve IC/BPS symptoms by lowering resting pelvic floor muscular tone (50). A study further showed that biofeedback has a good synergy with pharmacological treatment (51). Traditionally, biofeedback technique for IC/BPS focus on the fully pelvic floor muscle relaxation induced by maximum muscle contraction, but we find that maximum muscle contraction may aggravate the pain. Instead we recommend patients to practice the mild to moderate muscle contraction to promote pelvic floor muscle relaxation. Additionally, to maintain the therapeutic effect, it is also important to assign a home exercise to each patient. Based on our experience, approximate half of patients can get symptoms improvement after a scheduled 8 weeks treatment.

Yoga

Yoga is a mixture of physical and mental exercise that originated in ancient India. A systematic review showed that yoga can effectively relieve chronic pain in a variety of disorders (52). A study demonstrated that yoga can relax pelvic floor muscle through modulating relative muscular tone, which contributes to the IC/BPS symptoms relief (53). In terms of specific yoga postures, frog pose, fish pose, half-shoulder stand and alternate nostril breathing may be beneficial for IC/BPS (53).

Manipulative and body-based approaches

There has been sufficient evidence to suggest that pelvic floor dysfunction significantly contributes to the IC/BPS symptoms (54). Some complementary and alternative therapies attempts to manage IC/BPS symptoms through modulating pelvic floor muscular function.

Massage

Massage refers to a series of actions on the body with appropriate pressure to obtain muscular relaxation. Holzberg *et al.* (55) treated ten IC/BPS women using transvaginal massage focusing on levator ani, obturator internus, piriformis muscles and trigger point. After six therapeutic sessions, 90% of patients reported an improvement in pain and urinary symptoms. A prospective pilot study also evaluated the efficacy of transvaginal massage in 21 female patients with IC/BPS. These women were given transvaginal massage along coccygeus, iliococcygeus, pubococcygeus, and obturator internus for 10-15 times twice a week for 5 weeks. After the treatment, the ICSI and ICPI reduced from 8.9 to 6.9 and from 8.2 to 6.3 respectively, so did visual analogue scale for pain (5.4 vs. 3.5) (56). Besides transvaginal massage, we find that whole body massage can also be beneficial for IC/BPS patients. Based on our experience, about one third of patients can experience temporary symptom improvement after 4-6 sessions of full body massage. The possible mechanism could be the massage activates some specific brain regions, which down-regulates the influence of stress and negative emotion on body (57).

Physical therapy

Targeting the tension of pelvic floor musculature, some physical therapies have been used to treat IC/BPS. A pilot study showed that 94% of IC/BPS patients reported a symptoms relief and ICSI was decreased from 15.75 to 8.5 after 2 to 15 sessions of manual physical therapy (58). Another study demonstrated that manual physical therapy can significantly decrease the pelvic floor muscular tension (59). FitzGerald *et al.* (60) performed a multicenter, randomized, controlled trial comparing myofascial physical therapy to global therapeutic massage. After ten scheduled treatments, a significantly higher proportion (59%) of patients claimed moderate to marked improvement in myofascial physical therapy group compared to 26% in global therapeutic group, although both two therapies could relieve IC/BPS symptoms markedly. Based on this evidence, physical therapy may be more suitable for patients with high-tone pelvic floor dysfunction. Because it is non-invasive and easy to combine with other therapy, AUA guideline has listed physical therapy as the second line therapy (8).

Energy therapies

Energy therapies are an important component of CAM and

are helpful for maintenance of health. A systematic review demonstrated that Qigong and Tai Chi can improve physical function, boost immunity, relieve stress, and enhance quality of life (61). Despite lack of evidence on effect of energy therapies for IC/BPS, Qigong's efficacy on managing chronic pain has been reported (62). Functional MRI study revealed that Qigong can activate specific brain regions to suppress pain (63). On the other hand, a study showed that Qigong can relieve stress and anxiety (64), which may contribute to the improvement of IC/BPS symptoms. However, the efficacy of Qigong usually varies and depends on an individual's confidence in this form of energy therapy.

Whole medical systems

Traditional Chinese medicine

Traditional Chinese medicine refers to a system of medical practice originated in ancient China. Unlike the disease-targeted therapy of mainstream medicine, traditional Chinese medicine focuses on holistic healing which treats the individual based on the "syndrome differentiation" (65). Although the efficacy of traditional Chinese medicine for various diseases has been demonstrated, only a few case reports showed its effectiveness in IC/BPS. Due to lack of high quality evidence, further study is needed to assess the efficacy of traditional Chinese medicine on IC/BPS. However, individualized therapeutic model of traditional Chinese medicine makes design and implementation of clinical trial challenging.

Acupuncture

Acupuncture, as an effective therapy, has been accepted by urologists over the past decades (66). Our previous studies have shown that acupuncture can modulate bladder storage and emptying functions effectively (67,68). Only a few studies assessed the efficacy of acupuncture on IC/BPS. An early study reported that one patient got both subjective and objective improvement after acupuncture treatment (69). In a prospective study, eight patients with refractory IC/BPS were given acupuncture and moxibustion therapy once a week for 3 months (70). After treatment, three patients experienced a significant improvement and two of them had no symptoms recurrence during 48 months follow-up. Owing to only limited evidence available, further clinical trials are needed to determine the efficacy of acupuncture for IC/BPS. However, it remains a challenge to set up an

appropriate control in clinical trials of acupuncture, because no standard control therapy is available (71).

Summary

Despite limited available evidence, CAM therapies are relatively non-invasive and each therapy can certainly benefit a substantial group of IC/BPS patients. Because no definitive treatment is available and management of IC/BPS needs to balance potential benefit and adverse effects of treatment (72), the relative safety of CAM allows clinicians and patients to realize multimodal therapy for IC/BPS, which is recommended by the International Consultation on Incontinence Research Society (73). Moreover, miscellaneous CAM therapies also provide an opportunity for IC/BPS patients to practice an individualized therapeutic strategy. However, the target patient group of each CAM therapy needs to be further explored and defined. In addition, well-designed, randomized, controlled trials are also needed to provide more high quality evidence for the efficacy and reliability of CAM on managing IC/BPS.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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