

Painful bladder syndrome: management and effect on sexual function and quality of life

Zespół bolesnego pęcherza moczowego: leczenie i wpływ na funkcje seksualne oraz jakość życia

Schmid Corina, Berger Katrin, Müller Martin, Silke Johann, Mueller Micheal David, Kuhn Annette

Urogynaecology, Department of Gynaecology, University Hospital of Bern and University of Bern, Switzerland

Abstract

Objectives: Primary aim of this study was to evaluate the effect of our therapeutical management in patients with painful bladder syndrome (PBS) / interstitial cystitis (IC) on sexual function, quality of life and bladder symptoms using validated tools prospectively.

Material and Methods: A prospective case controlled study. The setting is a tertial referral centre. We included 69 patients with PBS/ IC according to the National Institute of Diabetes and Kidney Disease (NIDDK) into this study. All patients were managed applying determined therapeutical steps including tetracycline, bladder instillation consisting of heparine, local anaesthetic and natrium-bicarbonat, prednisolon and antihistaminics or instillation with DMSO.

Sexual function, quality of life and symptoms were evaluated with validated tools FSFI, King's Health Questionnaire and visual analogue scale (VAS).

Results: Pain, nocturia, urinary frequency and urgency were significantly reduced. The King's Health questionnaire showed a significant improvement of all domains but emotions and sleep, and FSFI improved significantly in all domains but orgasm.

Conclusion: Patients with PBS/IC undergoing defined therapeutical steps including tetracycline, bladder instillation and anti-inflammatory agents improved significantly regarding sexual function, quality of life and symptoms.

Long term follow-up has to prove this management as well as profound research on the unknown aetiology have to been done to determine even more efficient therapeutical regimes.

Key words: **painful bladder syndrome / treatment / sexual function / quality of life /**

Corresponding author:

Annette Kuhn
Urogynaecology, Department of Gynaecology, University Hospital Bern
Effingerstrasse 102
CH-3000 Bern, Switzerland
phone +41 31 632 10 10, fax: +41 31 632 12 51
email: annette.kuhn@insel.ch

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Streszczenie

Cel pracy: Podstawowym celem badania była ocena wpływu leczenia farmakologicznego, u pacjentek z zespołem bolesnego pęcherza moczowego (PBS - painful bladder syndrome) i śródmiąższowym zapaleniem pęcherza (IC - interstitial cystitis), na funkcje seksualne, jakość życia i objawy bólowe i dyzuryczne pęcherza moczowego przy użyciu walidowanych kwestionariuszy.

Materiał i metodyka: Prospektywne badanie porównawcze wykonano w szpitalu o trzecim poziomie referencyjności. Do badania włączono 69 pacjentek z PBS/IC spełniających kryteria NIDDK (National Institute of Diabetes and Kidney Disease). Wszystkie pacjentki leczono farmakologicznie włączając kolejno, w zależności od odpowiedzi klinicznej, tetracykliny, dopęcherzowe podawanie heparyny, lignokainy i dwuwęglanu sodu, prednizolon, leki antyhistaminowe lub DMSO (dwumetylosulfotlenek).

Funkcje seksualne, jakość życia i objawy chorobowe oceniono przy pomocy walidowanych kwestionariuszy: FSFI, Kwestionariusza King's Heath oraz wizualnej analogowej skali wzrokowej (visual analogue scale - VAS).

Wyniki: Ból, nokturia, częstotliwość oddawania moczu i parcia naglące były znacząco obniżone. Zgodnie z kwestionariuszem King's Heath wykazano znaczącą poprawę we wszystkich kategoriach za wyjątkiem emocji i snu, a w FSFI znacząco poprawiły się wszystkie kategorie za wyjątkiem orgazmu.

Wnioski: U pacjentek z zespołem bolesnego pęcherza moczowego, u których zastosowano terapie obejmujące kolejno: tetracykliny, leczenie dopęcherzowe i środki przeciwzapalne – wykazano znaczącą poprawę w zakresie funkcji seksualnych, jakości życia oraz ustępowanie objawów bólowych i dyzurycznych.

Długoterminowa obserwacja, tak samo jak rozszerzone badania nad nieznaną etiologią, muszą zostać przeprowadzone, aby określić bardziej efektywne modele terapeutyczne.

Słowa kluczowe: zespół bolesnego pęcherza moczowego / terapia /
/ funkcje seksualne / jakość życia /

Introduction

Painful bladder syndrome (PBS)/ interstitial cystitis (IC) is a clinical syndrome of pelvic pain and/or urinary urgency/frequency in the absence of a specific cause such as bacterial infection or bladder injury [1]. Mechanisms of PBS/IC are as yet undefined and it is largely this lack of knowledge, which precludes a systematic therapeutic approach. Painful bladder syndrome/ interstitial cystitis (PBS/IC) is a symptom complex of urinary frequency, urgency and /or chronic pelvic pain, in a patient in whom no other pathology can be established such as urinary tract infection, carcinoma or cystitis induced by radiation or medication. Considering the high number of patients in need of a permanent therapeutic regime (approximately 750 000 individuals in the USA, based on a survey by Curhan), the clinical problem of interstitial cystitis has a considerable impact – not only on the individuals' well being, but also on a Nation's health budget [2].

Pathophysiology of PBS/IC remains unknown, and as a consequence, the treatment of PBS/IC is largely empirical. A multitude of mechanisms of the disease have been postulated ranging from neuroinflammatory to autoimmune or possibly infectious or toxic agents. Recent studies have hinted towards a genetic course of the disease, but in most hypotheses an inflammatory component of some kind is considered important [3].

Several causes have been postulated including infection, autoimmune response, allergic reaction, neurogenic inflammation, epithelial dysfunction and inherited susceptibility.

The prevalence of painful bladder syndrome/ interstitial cystitis (PBS/IC) among gynaecological patients attending with unclear pelvic pain or chronic cystitis is higher than expected. The prevalence ranges from 10 to 500 cases/100000 women depending on the criteria used for diagnosis [4].

PBS has a known negative impact on quality of life and sexual function because of extreme urinary frequency and pain [5].

A large number of pharmacologic treatment options have been used to treat this condition with limited success including pentosan polysulfate, heparin, antihistamines, tricyclic antidepressants, intravesical dimethyl sulfoxide and bacilli Calmette-Guérin [6, 7, 8, 9, 10].

Objectives

The aim of this prospective cohort study was to show how our treatment algorithm based on current literature [7, 10, 11,12] affects sexual function, quality of life and symptoms in female patients with PBS.

Material and Methods

Patients were recruited from the outpatient department among of the Department of Urogynaecology at the University Hospital of Bern, Switzerland. All patients with the diagnosis of PBS/IC who gave informed written and oral consent were included into this prospective cohort study between July 2004 until October 2009.

The diagnosis of IC/PBS was made according to the criteria of the National Institute of Diabetes and Kidney Disease (NIDDK).

All patients had a history of unsuccessful therapy with anticholinergic agents, local estrogen if postmenopausal or even injections with Botulinum Toxin.

Patients filled in a three-day bladder diary and urinalysis was performed from midstream or catheter urine before inclusion.

Patients were examined gynaecologically to exclude local infection and transvaginal ultrasound was performed to exclude pelvic masses and patients were also asked to fill in a bladder diary assessing their functional capacity.

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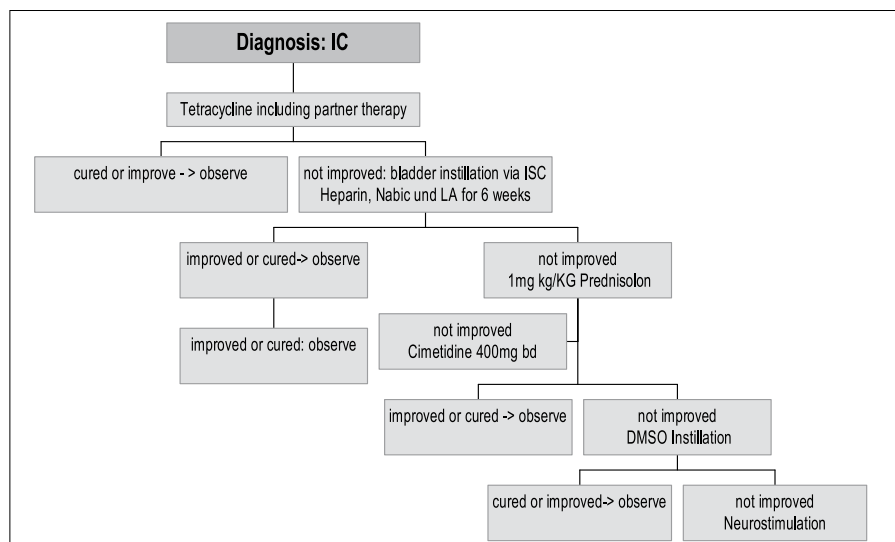


Figure 1. Treatment scheme.

Cystoscopy was performed using general anaesthesia and bladder distension was performed using a pressure of 80cmH₂O for 5 minutes, cystoscopic findings were noted. Cold cut biopsies were taken from suspicious lesions and sent for histology.

Treatment scheme was as follows: **Figure 1**

Tetracycline dosage was 100mg/d for two weeks followed by 100mg/d for additional two weeks including partner therapy. Condom use was recommended for the treatment period.

Instillation therapy was performed as followed:

Patients were instructed for intermittent clean self catheterization (ISC). 40000 IE Heparin, 10ml 1% Xylocain and 2ml Natriumbicarbonate were instilled twice a day for three weeks followed by once daily for another three weeks. For those who were unable to perform ISC, the district nurse was instructed to perform the instillation.

Prednisolon was given orally (1mg/kg) with an anti-ulcerative protection (aluminium hydroxide emulsion for four weeks after which the patients were weaned.

Cimetidine was administered orally 400mg bd.

DMSO is a chemical solvent with analgesic, anti-inflammatory and muscle relaxant effects. A total of 50ml Dimethyl Sulfoxide solution (DMSO), 500mg Dimethyl Sulfoxide per ml, were administered in six weekly instillations via ISC.

If these measures were not successful, patients were referred for neurostimulation.

At any time additional non steroidal antirheumatic agents (NSAR) or further pain medication were allowed if required.

The decision if to proceed to the next therapeutical step was performed by the patient: She was asked if she is satisfied with the current situation or if not; in the latter case, the next step was initiated. Treatment was defined as successful if the patients did not require further treatment. If relapse occurred after initial success the last successful step of the treatment scheme was repeated.

Patients were evaluated prior to the treatment and two weeks after each therapeutical step using the Female Sexual Function index FSFI, the King's Health questionnaire and the Visual Analogue scale (VAS).

Additionally, patients who were without any symptoms were asked to fill in the questionnaires six months after cessation of therapy.

To evaluate sexual function the Female Sexual Function Index (FSFI) questionnaire as determined by Rosen was used [13].

Six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction and pain) are determined and the questionnaire is validated in German, French and other European languages. Each domain is scored with scores ranging from 0-8. The higher the score the more sexually satisfied is the patient.

To assess quality of life the King's Health questionnaire was used [14]. The King's Health questionnaire is validated in several European languages and determines various aspects of quality of life as sleep, symptom bother, physical limitations, role limitations and emotions. The score ranges from 0-80. The higher the score the less bothered is the patient by the symptom.

To quantify the severity of the symptoms the visual analogue scale (VAS) 0-10 was used with 0 points being the least bother and 10 points being the worst possible bother of bladder symptom. Patients were asked to name their most bothersome symptom and to rate it applying the VAS.

For statistical analysis, Prism version 4.0 for Windows was used. A paired two-tailed t-test was performed to compare scores before and after treatment and alpha was set 0.05.

Results

72 patients could be included in the study and follow-up was 36 months (range 14-48).

Median age was 48 (range 24-62) years and a parity of 2 (range 0-3). The duration until the diagnosis of PBS/IC was 62 months (range 41-78) and previously performed cystoscopies were 2 (range 0-4).

21 patients had a history of endometriosis or were still undergoing investigations for endometriosis.

Functional capacity increased from 178ml (median; range 95-200ml) to 218 (median, range 145-260, p<0.01).

Table I.

Domain	Score before treatment, SEM	95% CI	Score after treatment, SEM	95% CI	p
Desire	2.2 ±0.17	1.83-2.57	5.0 ±0.18	4.62-5.38	<0.0001
Arousal	0.67 ±0.23	0.18-1.15	1.5 ±0.35	0.77-2.23	<0.03
Lubrication	2.78 ±0.58	1.55-4.03	2.77 ±0.56	1.59-3.97	0.89
Orgasm	1.28 ±0.19	0.89-1.69	1.33 ±0.14	1.04-1.63	0.413
Satisfaction	1.43 ±0.26	0.89-1.99	2.44 ±0.28	1.85-3.04	<0.001
Pain	0.56 ±0.2	0.13-0.98	5.68 ±0.11	5.43-5.91	<0.0001

Table II.

Domain	Score before Treatment, SEM	95% CI	Score after treatment, SEM	95%CI	p
General Health	42 ±0.6019	40.8-43.2	28 ±0.4815	27.04-28.96	<0.0001
Role limitations	58 ±0.3612	57.28-58.72	54 ±0.2408	53.43-54.57	<0.0001
Physical limitations	56 ±0.2408	55.52-56.48	48 ±0.2408	41.52-42.48	<0.0001
Personal Relations	54 ±0.2408	53.52-54.48	45 ±0.3612	44.28-45.72	<0.0001
Emotions	47 ±0.3612	46.28-47.72	49 ±0.3612	48.28-49.72	<0.001
Incontinence Impact	15 ±0.3612	14.28-15.72	14 ±0.2408	13.52-14.48	0.227
Sleep/energy	35 ±0.2408	34.52-35.48	23 ±0.3612	22.28-23.72	<0.0001

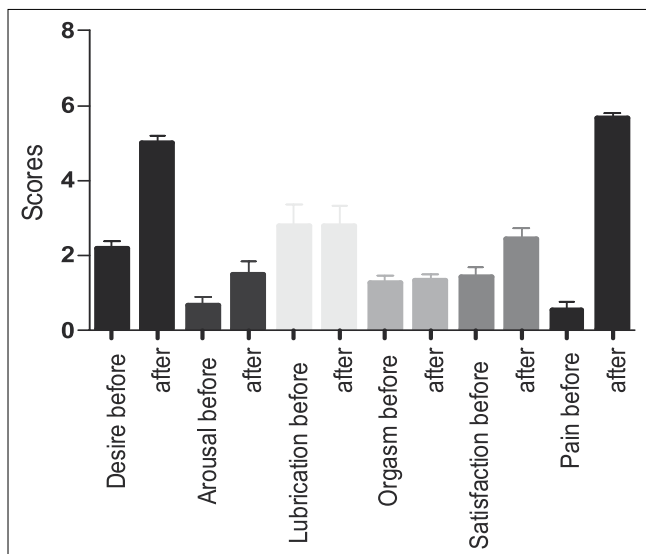


Figure 2. FSFI before and after treatment.

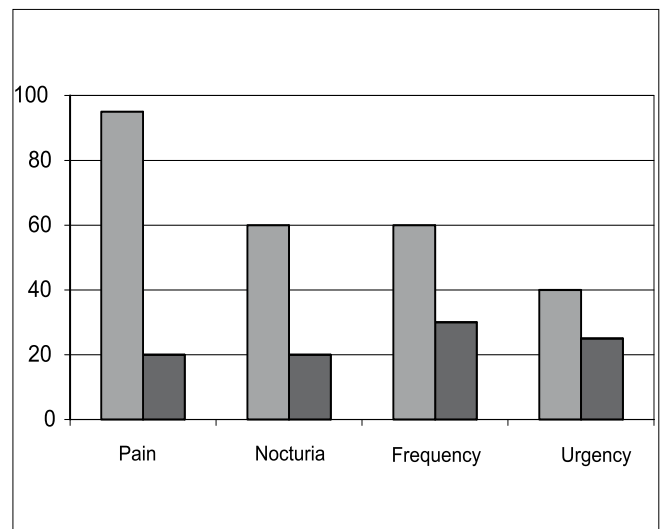


Figure 3. Most bothersome symptom as determined by visual analogue scale (VAS) before and after treatment

Treatment steps (followed the treatment scheme) and their success:

- 17 patients were satisfied after a treatment with Tetracyclines.
- 29 patients after therapy heparin, Xylocain 2% and Natriumbicarbonat,
 - nine patients after steroids,
 - two after antihistamines,
 - nine after DMSO-instillation.

- Six patients undergoing neurostimulation have not yet been followed up until now.

12 patients required repeat Heparin bladder instillation. Median symptom free interval was 6 months (range 3-24 months).

One patient required another drug therapy with steroids after 12 months and three repeated DMSO instillation after a median symptom free interval of 11 months (range 9-14 months).

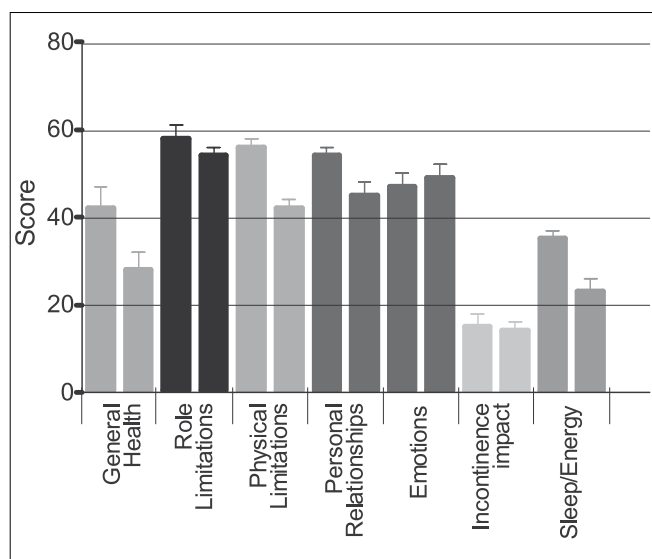


Figure 4. King's Health Questionnaire before and after treatment.

Patients did not experience serious side effects; one patient suffered from hot flushes during the use of prednisolone and two patients were suffering from recurrent bacterial cystitis while performing ISC for bladder instillations, which were treated with antibiotics.

Figure 2 shows the results of the FSFI questionnaire. The domains are marked in different colours with the initial FSFI score on the left side and the FSFI score three months after intervention to the right. For FSFI, a full data set of 66 patients only was analysed as three patients were reluctant to fill in the FSFI questionnaire.

Table I summarizes the statistical analyses of the FSFI scores before and after therapy.

Figure 3 shows the development of the most bothersome symptom as defined by VAS. Pain, nocturia, urinary frequency and urgency improved significantly ($p < 0.05$). Note that the higher the FSFI scores for pain are the less discomfort is noted.

48 patients named pain as the most bothersome symptom, 18 urgency, three nocturia and three patients were unable to name the most bothersome symptom.

Pain improved significantly ($p < 0.001$) as did nocturia ($p < 0.01$) and frequency ($p < 0.01$).

Urgency improved with a mean VAS score dropping from 40 to 25 but without statistical significance ($p = 0.09$; all student's t-tests).

Figure 4 shows the results of the King's Health questionnaire. On the left side the initial score of the King's Health questionnaire and on the right side the results six months after treatment.

King's Health Questionnaire scores in general showed high scores around 40 even after therapy for the domains role limitations, physical limitations, personal relationship and emotions; incontinence impact was low with 14 and 15 respectively.

Table II gives an overview about the statistical analyses of the King's Health Questionnaire results (all two-tailed t-tests).

General health, role limitations, physical limitations, personal relationship, and sleep/energy improved significantly. Emotions deteriorated significantly.

Discussion

The current study shows that with a stepwise therapy comprising tetracycline, bladder instillation with heparin/local anaesthetic, oral steroids, antihistamines and DMSO instillation an improvement of sexual function and quality of life in some domains but not in all can be achieved. 10% of patients who have not been evaluated yet have undergone neurostimulator implantation and did not respond to any of the therapeutical steps.

According to the King's Health questionnaire, incontinence impact in PBS/ IC-patients was low before and after treatment; this demonstrates that incontinence is not a major issue in PBS/ IC-patients.

Despite the common opinion that PBS/IC is easily confused with urinary tract infections and that consecutively antibiotics are of no therapeutic benefit [5], 25% of our patients responded to oral tetracycline therapy. Tetracyclines are broad-spectrum antibiotics that are effective against some of the most common infectious causes of sexually transmitted diseases, such as *C. trachomatis*, *N. gonorrhoea*, *U urealyticum* and *M. genitalium*. The prevalence of sexually transmitted disease is growing and in chlamydial infection it is 5-20% [15]. We might assume that in those patients who responded to tetracyclines an underlying infectious cause was the reason for the symptoms despite negative urine cultures.

Male partners of all patients were also treated, which is in accordance with the local guidelines for sexually transmitted diseases [16].

Particularly the complaint of pain as determined with the FSFI and the VAS can be effectively treated with the treatment scheme. 55% of the patients responded to either Heparin/LA or DMSO local bladder instillation, which corresponds to data from the literature [5; 7; 10].

In the current study, antihistamines were successful in three percent of patients only, which is remarkably less compared to data from Theoharides [11]. In the latter, hydroxyzine was used with an improvement of 65% and additive beneficial effects caused by sedative and anxiolytic properties were noted. Cimetidine as we used in the current study has been evaluated in small open-label trial [8] and has been shown to provide some relief. This was the reason why we included this drug in the current study; however, it has not been studied in randomized, placebo-controlled trials and the current data do not support a valuable effectiveness [9].

Only 13% of our patients felt cured after an oral therapy with prednisolone; this is less than in a small study of 14 patients with IC/PBS by Soucy who reported 69% improvement; however, in that study prednisolone was used as permanent medication which may be preferable in patients who respond to prednisolone [17].

Sexual dysfunction in PBS/IC patients is a known problem, and other studies have suggested the use of antidepressants [18].

Gardella describes that the use of antidepressants could have contributed to the preponderance of sexual dysfunction in her study group [19]. We have not used antidepressants in the current study; controlled clinical trials have not yet been performed but this may be an issue for future studies.

Sexual function is known to be impaired in women with interstitial cystitis as also shown in the current study [20]. Many women had pre-treatment FSFI scores below the cut-off score of 26 for hypoactive sexual disorder suggested by some authors to determine female sexual dysfunction [21].

While sexual dysfunction appears to be important in predicting quality of life, we cannot ascribe causality. Certainly sexual functioning in a chronic pain disease state as IC/PBS must be influenced by numerous variables that will include pain and storage symptoms associated with IC/PBS, but other factors, probably psychosocial, not yet described can possibly be involved as well. Further studies will address this association [22].

Five percent of patients were reluctant to answer the FSFI questionnaire; it is possible that most patients deciding not to answer that sexual function form may not have been sexually active or had been experiencing sexual dysfunction or were too embarrassed or distressed to complete the questionnaire [23].

We did not capture depressive symptomatology or coping strategies in our cohort of patients with IC/PBS. It has been reported that patients with IC/PBS suffer from greater depression than controls [24].

We did not perform multichannel urodynamics in this study, which is another potential negative aspect of the study. However, as all bladder interventions are painful for the patients we believe that the measurement of functional capacity, sexual function quality of life and symptom bother in PBS/IC patients using validated tools is more promising and less disturbing for the patient. Functional bladder capacity increased significantly. Cochrane database describes an increase of bladder capacity using intravesical oxybutinin instillation and but concluded that due to a lack of valuable data randomised controlled trials are still needed [25]. Regarding the academic aspect, we fully agree, however, it is difficult to suggest a patient who is suffering with diminished quality of life and sexual function a placebo controlled study.

The estimated prevalence of PBS/IC ranges widely, the pathogenesis is unknown, the diagnosis is usually delayed as demonstrated in our current study with a time interval between onset of symptoms and treatment of five years. The natural history is unclear, treatment is empiric, and preventive techniques have not even been considered [26].

Hanno summarizes: "The lack of universally accepted clinical diagnostic criteria of IC affects all aspects of making progress in understanding this disease". In the current study, we have used the criteria of the NIDDK because of rather clear criteria of inclusion and exclusion at the time of the study start despite not being the most recent classification [27].

We found the NIDDK criteria useful and easy in clinical practice; additionally, NIDDK criteria have a high specificity and have proven effective in clinical research studies allowing comparative analysis of results [12]. For future studies, ESSIC (European Society for the Study of interstitial Cystitis) criteria will be followed [28]. However, at the start of this study these were not available.

We did not experience any serious side effects of our treatment, and patients' acceptability of intermittent self catheterization (ISC) was not a problem despite their initial restraints about ISC. ISC does not appear to be a burden for the patient and, from a patient's perspective, can be recommended [29].

The origin of PBS/IC remains unclear, and the current study did not aim at investigating the pathogenic cause of PBS/IC. Consecutive projects for the determination of underlying molecular pathologies are planned.

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Disclosure of Interests

There is no conflict of interest of any authors except for the European Bladder Grant by Pfizer. All the authors contributed equally to the planning of the study (CS; KB, SJ; MDM; AK).

Ethical approval was obtained from the local ethics committee as uploaded (KEK Kantonale Ethikkommission Berne, Sitzerland, kek-bern.ch, President: Prof. Dr. pharm N. Tüller, Postfach 56, CH-3010 Berne, Switzerland). Studynumber: 146-05.

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