



Efficacy of instillation treatment with hyaluronic acid in relieving symptoms in patients with BPS/IC and uncomplicated recurrent urinary tract infections - Long-term results of a multicenter study

Ioan Scarneciu, Simona Bungau, Aura-Mihaela Lupu, Camelia C. Scarneciu, Ovidiu Gabriel Bratu, Orsolya Martha, Delia Mirela Tit, Lotfi Aleya, Sorin Lupu

► To cite this version:

Ioan Scarneciu, Simona Bungau, Aura-Mihaela Lupu, Camelia C. Scarneciu, Ovidiu Gabriel Bratu, et al.. Efficacy of instillation treatment with hyaluronic acid in relieving symptoms in patients with BPS/IC and uncomplicated recurrent urinary tract infections - Long-term results of a multicenter study. European Journal of Pharmaceutical Sciences, 2019, 139, pp.105067. 10.1016/j.ejps.2019.105067 . hal-02286095

HAL Id: hal-02286095

<https://hal.science/hal-02286095>

Submitted on 20 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**Efficacy of instillation treatment with hyaluronic acid in relieving symptoms in patients
with BPS/IC and uncomplicated recurrent urinary tract infections – long-term results of a
multicenter study**

Ioan Scarneciu^a, Simona Bungau^b, Aura-Mihaela Lupu^c, Camelia C. Scarneciu^d, Ovidiu Gabriel
Bratu^e, Orsolya Martha^f, Delia Mirela Tit^b, Lotfi Aleya^{g*}, Sorin Lupu^h

^aDepartment of Medical and Surgical Specialities, “Transilvania” University of Brasov, Brasov
Romania.

^bDepartment of Pharmacy, University of Oradea, Oradea, Romania.

^cDepartment of Radiology, Brasov CF General Hospital, Brasov, Romania.

^dDepartment of Fundamental, Prophylactic and Clinical Disciplines, “Transilvania” University of
Brasov, Brasov, Romania.

^eClinical Department 3, University of Medicine and Pharmacy “Carol Davila”, Bucharest,
Romania.

^fClinical Department of Surgery M5, University of Medicine, Pharmacy, Science and Technology
of Targu Mures, Targu Mures, Romania.

^gLaboratoire Chrono-environnement, CNRS 6249 Université de Franche-Comté, Besançon,
France.

^hClinic of Urology, Brasov Emergency Clinical Hospital, Brasov, Romania.

*Corresponding author: lotfi.aleya@univ-fcomte.fr

Laboratoire Chrono-environnement, CNRS 6249 Université de Franche-Comté, 16, route de Gray,
F-25030 Besançon cedex, France

Phone: + 33 (0) 3 81 66 66 66

Fax: + 33 (0) 3 81 66 57 97

Abstract

The purpose of this study is to evaluate the efficacy of intra-vesical instillations with hyaluronic acid (HA) in relieving lower urinary tract irritation symptoms in patients with urinary tract infections (UTIs) and bladder pain syndrome/interstitial cystitis (BPS/IC). This research, conducted in Romania, includes 30 patients with UTIs (Group I) and 24 with BPS/IC (Group II) as defined by European Association of Urology (EAU) Diagnostic Criteria. Data were collected prospectively, using pre- and post-treatment questionnaires for pelvic pain with a symptom scale for urination and frequency as well as visual analog scale (VAS) pain quizzes. At follow-up visits, at an average of 20 months, a significant improvement in urinary bladder pain, day-time urinary frequency and quality of life was observed in Group I patients. Group II patients experienced significant improvement in urinary bladder pain, urgency, nocturia and quality of life at the 15-month follow-up visit. Eighteen patients (75%) showed a complete response to intravesical HA instillations and required no further treatment. Our study demonstrates that intravesical HA instillations may be considered as an important treatment component, with long term positive effects in therapeutic strategy for optimal results in uncomplicated recurrent UTIs and BPS/IC, with good compliance and minimal side effects.

Keywords: hyaluronic acid; bladder pain; interstitial cystitis; urinary infection

1. Introduction

Uncomplicated recurrent UTIs are conditions just as incapacitating, expensive and frustrating, for patients and medical staff alike. Almost 50% of all women will have UTIs during their lifetime and for 33% this happens before the age of 24. Up to 35% of UTIs will repeat within 3-6 months (Foxman, 2000; 2002). An uncomplicated UTI is defined as an infection that occurs in a healthy person in the absence of structural or functional abnormalities of the urinary tract. Recurrent uncomplicated UTI may be defined as 3 or more uncomplicated UTIs within 12 months (Hooton, 2001; Zhong et al., 2011). Also, the elevated incidence of this disease is associated with high cost due to the repetitive use of many antibiotics and other treatments, as well as to multiple visits to GPs, gynecologists or urologists (Foxman, 2002; Ronald 2002; Raymond et al., 2012).

BPS/IC is a heterogeneous chronic disabling condition affecting the patient's quality of life and provoking a medical condition necessitating diagnosis and treatment. Over time, numerous names, definitions, and classifications of this condition have been proposed. According to the Society for Urodynamics and Female Urology this affliction is characterized by an unpleasant sensation of pain, discomfort and pressure felt in the region of the bladder and is associated with lower urinary tract symptoms present for at least 6 months prior to diagnosis, while urinary infection or other possible identifiable causes are excluded (Hanno et al., 2010; Tit et al., 2017). Though there is no general agreement on the exact pathophysiology of this disease, in many cases a disorder of the barrier between the urine and the mucous membrane of the bladder appears to be the mechanism underlying symptom function and manifestations (Hanno et al., 2010; Magnus et al., 2008).

The wide margins in prevalence reported by different authors for BPS/IC lead to an accepted range of 10-530/100000, a broad interval which reflects a reasonable consensus in reporting the pathology (Fall et al., 2008; Rovner et al., 2000). A deficiency is assumed to be present in the

protective layer of glycosaminoglycans (GAG), the lining of the bladder epithelium which is a common path in development of BPS/IC and recurrent UTIs (Constantinides et al., 2004; Stav et al., 2011). Glycosaminoglycan is an important component of the protective liner, the deficiency being documented in a series of studies on painful bladder syndrome (Hurst et al., 1996), mainly using a positive potassium chloride sensitivity (PST) or the Parson test and the favorable response obtained to GAG restorer agents (Parsons et al., 1991; Daha et al., 2008).

Various techniques (instillations with chondroitin sulphate, heparin, pentosane polysulphate and HA) for recovering the layer of GAG from the bladder mucosa level have been used with differing results. Iavazzo et al. (2007) have shown a varied but positive response (30 to 73%) in patients with BPS/IC when instillation with HA was used (Leppilahti et al., 2002; Iavazzo et al., 2007). In patients with recurrent UTIs, Constantinides et al. (2004) obtained promising results with HA, 70% of patients being without recurrence at an average follow-up of 12.4 months. Treatment with HA was first used with favorable results in patients with BPS/IC and the indication was later extended to other conditions for which instillation was shown to be effective (recurrent UTIs or radiation-induced cystitis). When trying to restore the protective barrier of the bladder by agents with GAG substitution role, doctors encounter great difficulty as therapeutic agents are numerous, with controversial results, and since adequate studies proving efficiency are lacking (Rovner et al., 2000; Burkman, 2004). An optimal therapeutic regimen should be based on its ability to relieve symptoms, improve patients' quality of life and diminish costs (Burkman, 2004). Products available in Europe and currently used for instillations in the treatment of BPS/IC are listed in **Table 1**.

Our research was a prospective, open and non-randomized study conducted in Romania over a period of 2 years. The long-term efficacy of instillation treatment with sodium hyaluronate (the

only product available on the Romanian pharmaceutical market at the beginning of the study) was evaluated separately in relieving lower urinary tract irritation symptoms in uncomplicated recurrent UTI and BPS / IC patients; we considered that HA treatment to be potentially beneficial since the short-term progression (after 4-6 instillations) proved to be positive, fact specified as well in the product prospectus and documented in numerous investigations. There are few studies evaluating the efficacy of HA instillation in these types of pathologies and the number of patients enrolled in existing trials is small / insufficient (9 patients in Leppilahti's et al. study, 40 patients in Constantinides's et al. study, and in the study according to Iavazzo et al. (which is actually a review of 9 other studies), the number of patients is still very low (Leppilahti et al., 2002; Iavazzo et al., 2007; Constantinides et al., 2004). The results remain contradictory due to this small number of patients in each study, especially when the treatment is prescribed for urinary infections. Also, the recommendations are still under discussion and the conclusions remain unclear because of the same causes (few studies, small number of patients).

2. Material and methods

2.1. Study Design

The study was conducted from January 1st, 2016 through March 2018, in 3 university centers, located in Romania (Clinic of Urology – Emergency Clinical County Hospital of Brasov, Clinic of Urology – “Dr. Carol Davila” Central Military Emergency University Hospital of Bucharest, and Clinic of Urology – Emergency Clinical County Hospital of Targu Mures) on 54 women, divided into two groups: 30 who had uncomplicated recurrent UTIs (Group I) and 24 who had BPS/IC (Group II) according to EAU Diagnostic Criteria (Engeler et al., 2018).

The inclusion criteria of the patients in the study were as follows:

For Group I: patients over 18 years, with recurrent and symptomatic uncomplicated UTIs (dysuria, frequency, urgency, haematuria), with positive urine cultures, after more than 6 months of different types of treatments (prescribed for the specific condition).

For Group II: patients over 18 years, fulfilling the EAU criteria for BPS/IC (Engeler et al., 2018): history of cystoscopy/hydrodistension with a diagnosis of IC confirmed by findings of Hunner's ulcer or glomerulation, symptoms of bladder pain and urinary urgency (for at least 6 months), urinary frequency (at least 8 times a day), nocturia (at least twice a night), symptoms not significantly relieved by antimicrobial agents, anticholinergic drugs, or antispasmodics, pain, pressure or discomfort associated with the urinary bladder (despite current therapy).

The exclusion criteria that our study considered, were:

For Group I: signs of complicated UTI, conditions possibly leading to complicated infections (i.e. renal diseases, patients with urinary catheter), pregnancy/breastfeeding, current self-medication with other treatments for UTI, antibiotic use in the last 7 days, contraindications for instillation treatment with HA, serious diseases, inability to understand the study design, current or past participation (within the last 6 months) in a clinical trial.

For Group II: patient currently pregnant or breastfeeding, intravesical therapy or bladder hydrodistention within the previous 60 days, history of augmentation cystoplasty, cystectomy, neurectomy, history of ureteral reflux, evidence of renal impairment (creatinine > twice the upper limit of normal at first visit, hepatic impairment (AST or ALT >3 times the upper limit of normal at first visit, clinically significant cardiovascular, respiratory or psychiatric diseases, urinary tract infection within the past 3 months prior to study entry, active genital herpes or vaginitis, uterine, cervical, vaginal, or urethral cancer within the past 5 years prior to entering the study, history of cyclophosphamide or chemical cystitis, urinary tuberculosis or radiation cystitis, history of bladder

tumors, inability to understand the study design, current or past participation (within 6 months) in a clinical trial.

Patient distribution was according to the diagnosis, risks and benefits of the indicated treatment.

In both groups, they were comparable in age and gender. All data were prospectively collected, stored and processed; also, all steps necessary to establishing the correct diagnosis and potential treatment were respected.

All the patients (in both groups) received intravesical HA instillations in doses of 50 mL / 40 mg after the bladder was emptied. Subjects were advised to maintain the instilled substance in the bladder for a minimum of 30 minutes, but preferably for 1-2 hours (following the product guidelines). The procedure was initially carried out once a week over a period of 4 weeks and then continued once every month (for 23.4 ± 5.92 weeks for Group I and 21.9 ± 8.79 weeks for Group II). Group I (30 patients) received a low dose of an antibiotic, while Group II did not. Patients were evaluated throughout the treatment period and post-instillation clinical parameters were monitored at 15-20 months following treatment, with placement of therapeutic effects taking place over time.

2.2. Clinical investigations

All patients received pre- and post-treatment questionnaires ("The Pelvic Pain and Urinary/Frequency Patient Symptom Scale Questionnaires" (PUF)) to assess their symptoms. Urodynamic studies were performed in all patients in both groups in order to exclude any other pathological cause of the symptoms. The PUF questionnaire, developed by C. Lowell Parsons, is a rapid and informative diagnostic tool used to screen patients with chronic pelvic pain; it uses a symptom score (which measures how often a patient experiences problems) and a bother score (which notes the degree to which the symptoms bother the patient); the bother and symptom score

combine for a total PUF score. Scores range from 0 to 35; a score greater than 12 is considered indicative of significant symptoms (Parsons et al., 2002; Brewer et al., 2007). Twelve patients (40%) in Group I showed evidence of detrusor hyperactivity (OAB) in urodynamic tests, while the remaining 18 patients had a normal urodynamic evaluation. All patients in Group II presented urodynamic evaluations confirming the absence of OAB and additional parameters meeting the criteria for inclusion of EAU diagnostic data.

Pain was assessed using a visual analog scale (VAS), and quality of life was also evaluated. In pain research VAS remains one of the most commonly used measures of pain intensity. Nevertheless, questions remain concerning interpretation of results (Jensen et al., 1986; Burckhardt and Jones, 2003). VAS is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line, usually 100 mm in length, anchored by 2 verbal descriptors, one for each symptom extreme (Jensen et al., 1986). Though no consensus exists, the following cut points on the pain VAS are recommended: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm) (Jensen et al., 2003).

For the quality of life evaluation, we used The Quality of Life Scale (QOLS), a questionnaire created by John Flanagan in 1970 and designed as a 15-item instrument that measured five conceptual domains of quality of life: 1) material and physical well-being; 2) relationships with other people; 3) social, community and civic activities; 4) personal development and fulfillment; 5) recreation. A new item was later introduced: independence (the ability to do for yourself). Thus, for this study we used the 16-item questionnaire since it is considered one of the most powerful scales for measuring quality of life. A validated questionnaire, quick and easy to use, the QOLS is scored by summing the items for a total score, ranging from 16 to 112. A higher score indicates a

higher quality of life, but a score of 90 is accepted as the average in healthy populations (Burckhardt et al., 2003).

Ultrasound bladder volume calculation was also used in this study since it represents a simple method to estimate the bladder volume. Every patient was examined with the same ultrasound scanner, the examination being performed by the same specialist. The sets of data concerning the volume were obtained using 3D ultrasound equipment, as well as a motorized curved array transducer (2-5 MHz). The ultrasound probe was fixed about 2 cm on longitudinal and transverse planes and the bladder diameters (anteroposterior, transverse and superoinferior) were measured. Based on these data, bladder volume was automatically determined. The normal volume of a bladder is between 300 and 500 mL, with variations depending on sex, height and weight. The damage degree from inflammatory causes of the bladder is also evaluated according to the capacity of the bladder. In other words, the more severe the impairment the smaller the volume of the bladder (its capacity), the patient having to urinate smaller amounts of urine more frequently.

Our research followed the evolution of the symptoms of the patients included in the study, and this goal can only be achieved by using subjective tests related to symptomatology (not objective tests). Also, the scales used (PUF, VAS and QOLS-16) are the most important, recommended and used worldwide in assessing the symptoms of various diseases or treatments.

2.3. Statistical Analysis

Statistical analysis was performed using EpiInfo and SPSS. The average parameter values, standard deviations, frequency ranges, and statistical significance tests were calculated using the Student method (t-test). The Mann Whitney U test (Wilcoxon–Mann–Whitney test) was used to describe and evaluate pre-instillation parameters of both groups. The Bravais–Pearson correlation

coefficient or Pearson product-moment correlation coefficient (PPMCC) were used to calculate an independent indicator of the units of measurement of the two variables. When the p-value was below the conventional 5 % ($p < 0.05$) the correlation coefficient was accepted to be statistically significant.

2.4. Ethical Statement

Each patient signed an informed consent form prior to inclusion in the study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki, and in respect of ethical principles for medical research involving human subjects, approved by the Ethics Committees of the Emergency Clinical County Hospital of Brasov, of the Central Military Emergency University Hospital of Bucharest, and of the Emergency Clinical County Hospital of Targu Mures.

3. Results

3.1. Patient base-line (pre-instillation) parameters

Pre-instillation demographic parameters were statistically comparable in the two groups. Group I patients were 19 to 69 years old (average age: 45), while Group II included patients from 35 to 81 years (average age: 52). Gender distribution was 0:30 for Group I and 0:24 for Group II, as presented in **Table 2**.

One patient in Group I, initially included in our study, was later excluded due to an associated pathology (exclusion criteria) requiring surgery that resulted in placement of a ureteral "JJ" stent, the presence of the stent being considered as a possible cause of inferior urinary tract symptoms

and bladder pain syndrome. The classic Hunner ulcer at cystoscopy was observed in only 7 patients.

Each patient received from 4 to 18 instillations (an average of 9 instillations). **Table 3** presents the characteristics of treatment parameters.

3.2. Patients' post-instillation parameters

3.2.1. Bladder pain

Data was collected prospectively using the pre- and post-treatment questionnaires for pelvic pain, with a symptom scale for urination and frequency as well as the VAS pain quizzes. For Group I significant improvement in urinary bladder pain was observed at an average follow-up of 20 months. A statistically significant difference (Mann Whitney U test with $p=0.0007$) in pain reduction on the VAS was seen from 7.56 ± 0.41 (pre-instillation) to 3.23 ± 0.69 (post-instillation). Group II experienced a significant improvement in urinary bladder pain, reported a reduction in pain-related symptoms on the VAS from 8.23 ± 0.35 to 3.99 ± 1.02 (Mann Whitney U test with $p=0.0235$).

3.2.2. Daytime urinary frequency

For Group I significant improvement in daytime urinary frequency was observed, being reduced from 10.38 ± 1.44 to 7.88 ± 1.41 (Mann Whitney U test with $p=0.0423$). In Group II, no statistically significant change was found for daytime urinary frequency post-treatment, as a reduction was reported from 11.66 ± 1.75 (pre-treatment) to 7.62 ± 0.88 (post-) (Mann Whitney U test with $p=0.4013$).

3.2.3. Quality of life

An important parameter for these patients, quality of life shows significant improvement in Group I, from 80 ± 11.2 to 96 ± 12.4 , after treatment (Mann Whitney U test with $p=0.0322$). Group II also

experienced significant improvement in the quality of life, from 78 ± 12.4 to 95 ± 11.9 (Mann Whitney U test with $p=0.0487$).

3.2.4. Urgency

At the end of treatment, no statistically significant change was observed for urgency among Group I patients: from 6.33 ± 0.81 (pre-treatment) to 4.02 ± 0.62 (post-treatment) (Mann Whitney U test with $p=0.0693$). Group II, however, experienced a significant improvement in urgency, from 8.57 ± 0.61 to 4.9 ± 0.86 (Mann Whitney U test with $p=0.0252$).

3.2.5. Nocturia

For Group I no statistically significant change was observed regarding nocturia, this parameter being only slightly modified by treatment, from 4.10 ± 0.56 to 4.07 ± 0.88 following patient evaluation (Mann Whitney U test with $p=0.9075$). Group II clearly benefited from treatment, experiencing significant improvement in nocturia, from 3.05 ± 0.52 to 1.57 ± 0.41 (Mann Whitney U test with $p=0.0243$).

3.2.6. Bladder volume change

Treatment with HA instillation had no significant effect on bladder volume in either group. For Group I, the volume was modified from 251.2 ± 4.5 to 322.5 ± 41.69 following treatment, and for Group II from 185.4 ± 15.55 to 258.30 ± 41.21 (Mann Whitney U test with $p=0.7782$ for Group I and $p=0.3027$ for Group II). Treatment duration for Group I was 23.4 ± 5.92 weeks, with patient monitoring for 19.9 ± 5.98 months afterwards. Eighteen patients responded to treatment (60%) while 12 showed no response (40%). Of those who did not respond, 6 patients (50%) continued to receive low-dose prophylactic antibiotic therapy. Six patients with OAB and recurrent UTIs were advised for other therapeutic solutions, including radical surgery with a urinary derivation (ileal conduit). In Group II, 18 patients (75%) showed complete response to intravesical HA and required

no further treatment, while 6 (25%) showed no response. Treatment duration was 21.9 ± 8.79 weeks, with continuous monitoring for 15.23 ± 6.88 months afterwards. Three patients were oriented towards other therapeutic solutions, including radical surgery with a urinary derivation (ileal conduit), while 3 others were given intravesical injections of botulinum toxin. Side effects reported by patients were mild, consisting of bladder irritation (6 patients in Group I and 4 in Group II); no patient interrupted the treatment.

For recurrent UTIs, after applying the t-test significant differences $p < 0.05$ were found as to pain score, day-time frequency and life quality while in rest there are no significant differences ($p > 0.05$). Evolution of data before and after instillation is plotted in **Figure 1** and the patient's evolution in time is illustrated in **Figure 2**. For IC/PBS interstitial cystitis, we obtained significant differences ($p < 0.05$) in the case of pain score, life quality, urgency and nocturia while in rest no significant differences were found. The p values were obtained by applying a t paired test and the results are plotted in **Figure 3** and **4**.

4. Discussion

Recurrent UTIs are common in general gynecology or urology consultation services and affect all patient age groups (Dason et al., 2011). It is estimated that 50 to 60% of women will experience at least one episode of urinary infection during their life (Czaja and Hooton, 2006; Epp and Larochelle, 2010). These infections are more common in women than in men, and the costs of treatment and care are substantial (Smelov et al., 2016). Also, antibiotic use as a treatment for such infections is a key driver in reinforcing resistance to antibiotics and has become a substantial problem in modern medicine in general (Costelloe et al., 2010).

Current treatment options include the use of prophylactic antibiotics (Zaha et al., 2019), estrogen replacement therapy in postmenopausal women (Epp and Larochelle, 2010; Smith et al., 2018; Vahlensieck et al., 2016), cranberry juice (antioxidants) (Epp and Larochelle, 2010; Jepson et al., 2012; Yeung et al., 2019) and lifestyle change (Epp and Larochelle, 2010; Jhang and Kuo, 2017) which involve increased fluid consumption, more frequent emptying of the bladder, especially before and after sexual activity, supplementary vitamin D (Hertting et al., 2010) plant disinfectants and plant diuretics (Wagenlehner et al., 2013), acidification of urine (Vahlensieck et al., 2016), immune active prophylaxis (47), prophylaxis with probiotics (*Lactobacillus* spp.) or D-mannose (Vahlensieck et al., 2016). Antimicrobial prophylaxis should be considered just following the other measures due to risk of adverse events and collateral damage. Antimicrobial prophylaxis can be administered continuously (daily, weekly) for 3 or 6 or 12 months, or as a single post-coital dose (nitrofurantoin, TMP, TMP/sulfamethoxazole, quinolone or other treatments) (Epp and Larochelle, 2010; Vahlensieck et al., 2016; Zaha et al., 2019).

None of these options have been proven to produce long-term results. In addition, the most effective treatment (antimicrobial treatment or prophylaxis) is associated with many adverse events and side effects. Also, patient compliance with the treatment tends to decrease over time (Epp and Larochelle, 2010; Vahlensieck et al., 2016; Wagenlehner et al., 2013; Beerepoot et al., 2013). Among the general population, recurrent UTIs cause substantial costs, but on a personal level this pathology is accompanied by considerable impact on the quality of life (Ciani et al., 2016). In these cases, gentamicin instillation treatment is also recommended, with good though questionable results (Ablove et al., 2013; Cox et al., 2017).

Due to the poor long-term results obtained with other treatments, a new type of treatment was suggested based on the recovery of the GAG layer (Lazzeri and Montorsi, 2011). For this purpose,

some authors have suggested the use of heparin instillation, with encouraging results in reducing UTIs recurrences (Vij et al., 2012; Ablove et al., 2013). Also, combined HA and chondroitin sulfate (CS) instillations appear to produce good results (Ciani et al., 2016; Damiano et al., 2011). Some publications can be found in the literature on the intravesical use of HA for treatment of recurrent UTIs. Glycosaminoglycan (GAG) deficiency in the urinary bladder epithelium is a convincing factor in the etiology of recurrent UTIs (Rovner et al., 2000, Constantinides et al., 2004; Damiano et al., 2011; Bumbu et al., 2016; Abdel-Daim et al., 2019). Constantinides et al. (2004) conducted a pilot study on forty women, treated with HA instillations for recurrent UTIs in 2004, obtaining no recurrence for five months, and 70% of patients had no recurrence at a one-year follow-up visit. The average time to recurrence was approximately 17 months post-treatment, with high tolerability. Lipovac et al. (2007) practiced HA instillations for more than 6 months (9 instillations) on 20 women with recurrent UTIs and showed a reduction in the number of recurrences per person and per year, from statistically significant results, with an increasing time to recurrence of up to 178 days after treatment. Some authors (Sharifiaghdas and Hamzehi, 2010) conducted a study on thirty women with recurrent UTIs and reported good results, with no recurrence 6 months after treatment. Other authors have also reported good results with HA instillations, but those studies were conducted only on small groups of patients (Vedanayagam et al., 2013, Nightingale et al., 2018).

We recruited 30 patients with documented recurrent UTIs who were on prophylactic antibiotic therapy during the study period. On average, each patient received 9 intravesical HA instillations over 23 weeks. At a follow-up visit an average of 20-months post-treatment, 60% of our patients demonstrated complete response and interrupted the prophylactic antibiotic treatment. Of those who did not respond to treatment, 20% continued the low-dose prophylactic treatment. Six patients

with OAB and recurrent urinary tract infections were re-oriented to other therapeutic solutions. Also, after the HA instillations, patients with recurrent UTIs showed many other statistically significant improvements: bladder pain, day-time frequency and quality of life. The other parameters – urgency, nocturia and bladder volume change – showed no significant post-treatment change. Side effects reported by patients were mild: bladder irritation (6 patients) with no interruption of treatment.

BPS/IC is a condition affecting both women and men, with no variation according to race or ethnicity (Clemens et al., 2007). Its prevalence is difficult to appreciate as no clear definition or criteria for diagnosis can be established; it is thus considered to be an underdiagnosed affection (Berry et al., 2011; Mullins et al., 2015) and is estimated to affect from 2.7% to 6.53% of persons aged 18 or older (Berry et al., 2011).

Recognized as difficult to establish, the diagnosis is based in particular on the symptoms described by the patient after eliminating other causes that may induce symptoms (Clemens et al., 2007; Hanno et al., 2010). Though the term “interstitial cystitis” is frequently reserved for cases of BPS associated with typical cystoscopic and histologic findings, the term IC is primarily used to describe inflammatory changes localized in the bladder. The term BPS was initially used to describe patients with painful bladder symptoms, though such symptoms may also have other causes. However, in the absence of other causes that might help to explain these manifestations (van de Merwe et al., 2008; Han et al., 2018) the two terms are often used together to describe a pain syndrome that is mainly located in the bladder and pelvis in relation to bladder filling. Symptoms are numerous and unspecific. It is recognized that patients generally describe pain that is localized in the bladder, pelvis and genital organs, and that is accompanied by urinary symptoms (dysuria, frequency), in the absence of proven urinary infection or other obvious pathologies (van

de Merwe et al., 2008; Hanno et al., 2010; Mullins et al., 2015; Han et al., 2018). However, the diagnosis is difficult to establish because BPS/IC can be confused with many other pathologies (Leppilahti et al., 2002; van de Merwe et al., 2008).

Despite all the research, clinical trials and repeated attempts made to understand the mechanism of these conditions, BPS/IC is still insufficiently known and effective treatment remains under debate. Numerous problems have been caused by the fact that, besides pathological mechanisms of the bladder, it supports the existence of other possible mechanisms located outside of the bladder (pelvic or systemic, including alterations of the central nervous system in some patients) that may be determinant for BPS/IC (Mullins et al., 2015; Engeler et al., 2018). To further complicate matters, epidemiological studies have shown that BPS/IC is commonly associated with many other chronic conditions which may be caused by the same physio-pathological mechanism (systemic mechanism) and that the essential problem might not be located in the bladder. Frequent associations are with fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and chronic widespread pain (Mullins et al., 2015). This organ-centric terminology places BPS/IC within the overall scope of chronic pelvic pain syndromes (CPPS), which also include prostate, gynecological and bowel pain syndromes. The European Association of Urology no longer recommends the use of terms such as BPS/IC (or other types of pain syndromes) and now groups them all together under the more generally diagnostic term Chronic Pelvic Pain Syndrome (CPPS) (Engeler et al., 2018), though this practice is not universally accepted.

Though consensus and convincing data are lacking, certain risk factors for BPS/IC are nevertheless recognized: genetics, psychological state, recurrent physical trauma and endocrine factors (Engeler et al., 2018). In urological clinical practice, BPS/IC and recurrent UTIs can be difficult conditions to manage. According to the European Association of Urology, BPS/IC is described as a chronic,

annoying condition of the bladder (Engeler et al., 2018) and the so-called Hunner ulcer may be a typical cystoscopic finding in from 10 to 50% of IC patients, which is why the absence of Hunner lesions is not a criterion for exclusion of BPS/IC (Hanno et al., 2010).

Diagnosis is based primarily on patient symptoms, after exclusion of other causes. Investigations directed towards differential diagnosis are recommended, but other tests are also needed: cystoscopy, urodynamics, pathology exam (during cystoscopy), potassium test (Hanno et al., 2010; van de Merwe et al., 2008; Grigorescu et al., 2016; Engeler et al., 2018). Biomarkers will be recommended in the future as they can furnish important data, especially an anti-proliferative factor (Grigorescu et al., 2016).

Cystoscopic bladder biopsy studies revealed clear defects in the urothelial GAG layer, with secondary occurrence of submucosal exposure to toxic substances in the urine, with cytotoxic effect (Constantinides et al., 2004; Logadottir et al., 2004; Sanchez-Freire et al., 2011; Stav and Lindner, 2011; Engeler et al., 2018). Not without significance is the fact that many studies show that BPS/IC has a significant impact on quality of life, with consequent depression, anxiety, impaired emotional functioning, insomnia and fatigue, including change of profession due to pain (Bosch and Bosch, 2014; Chuang et al., 2015; Engeler et al., 2018). Different conservative therapies have been suggested for BPS/IC: physiotherapy, behavioral modification, stress reduction, dietary manipulation, all with different and inconstant results (van de Merwe et al., 2008; Hanno et al., 2010; Engeler et al., 2018).

Types of surgical and medical treatment have been previously described in the literature for this condition with varying results (Porru et al., 1997; Constantinides et al., 2004; Iavazzo et al., 2007; Fall et al., 2008; Gajewski and Al-Zahrani, 2011; Engeler et al., 2018; Han et al., 2018). These include oral hydroxysin, pentosan, amitriptyline, L-arginine, methotrexate, montelukast,

416 prostaglandins, cyclosporin A, oxybutynin, duloxetine, intravesical pentosan, intravesical
 417 *Botulinum toxinum* type A, intravesical anesthetics, intravesical heparin, intravesical *Bacillus*
 418 Calmette-Guerin, intravesical silver nitrate, intravesical chondroitin sulphate, intravesical
 419 dimethylsulfoxide (DMSO), intravesical cloropactin WCS 90, intravesical vanilloids, intravesical
 420 HA and many other possible substances (many of which have no demonstrated efficacy). Surgical
 421 interventions include bladder distention, hyperbaric oxygen, epidural pain pumps, sacral
 422 neuromodulation, sympathetic denervation, transurethral resection and electrocoagulation or
 423 major reconstructive surgery (Magnus et al., 2008; Fall et al., 2008; van de Merwe et al., 2008;
 424 Hanno et al., 2010; Gajewski and Al-Zahrani, 2011; Engeler et al., 2018; Han et al., 2018).
 425 Instillation treatment with HA has found its logical explanation via attempted restoration of the
 426 GAG layer, which is affected primarily in this pathology, the short-term response being favorable
 427 in many situations. Many authors have published studies of different groups of patients, with
 428 differing results. In patients with BPS/IC, Iavazzo et al. (2007) have shown a varying but positive
 429 response ranging from 30 to 73 %, when instillation with HA was used. Kallestrup et al. (2005)
 430 observed a decrease in nocturia and pain of 40 and 30 %, respectively, in 65 % of responders to
 431 therapy with minimal side effects and with a decrease in analgesic use after 3 months of HA
 432 instillation treatment. In 2015, an interesting study by Rooney et al. (2015) highlighted the
 433 mechanisms through which HA instillation is efficient in BPS/IC treatment, proving that HA
 434 significantly decreases induced cytokine secretion (4-5 folds increase), increases sulphated GAG
 435 production (2-fold increase) and decreases trans-epithelial permeability. They also suggested that
 436 HA pathway is a clinical target and potential treatment vector (Rooney et al., 2015). In a study
 437 from 2016, Pyo and Cho (2016) concluded that HA instillations (alone or in combination with CS)
 438 have good and significant effects on pain symptoms, quality of life and other outcomes. The study

by Riedl et al. (2008) is probably the most extensive for this purpose (in terms of number of patients): one hundred twenty-six patients with BPS/IC were enrolled. The authors observed a VAS score of 8.5 which decreased to 3.5 after therapy; 55 % of patients remained with no or minimal bladder symptoms and 84% reported significant post-treatment improvement in their quality of life. In addition, they suggested that the HA instillations would have a good response rate if a modified potassium test showed a positive result (sign of a urine-tissue barrier disorder). Some authors have suggested administration of HA with EMDA (electromotive drug administration) as this technique appears to improve treatment efficacy (Gülpınar et al., 2014). Another contradiction is observed concerning different regimens of intravesical HA instillation for patients with BPS/IC. Lai et al. found no significant difference in therapeutic effect between two groups of regimens, both showing significant improvement in symptom scores and quality of life (Lai et al., 2013). All these studies have proven that HA treatment acts on the GAG barrier, not only by restoring it momentarily, but with its ability to stimulate the formation of new cells to regenerate the GAG layer.

24 patients with BPS/IC were recruited for our study according to the EAU Diagnostic Criteria. On average, each patient received 9 intravesical HA instillations over nearly 22 weeks. After a follow-up period of 15 months, 75 % of these patients demonstrated a complete response. Six of them (25 %) did not respond to this treatment and thus other therapeutic solutions were prescribed, including radical surgery with a urinary derivation (n=3) and intravesical *Botulinum* toxin type A (n=3).

Some patients with BPS/IC showed other improvements following the HA instillations; statistically significant improvements were observed in pain, urgency, nocturia and quality of life. Other parameters, such as day-time frequency and bladder volume were not significantly modified.

Side effects reported by patients were mild and consisted of bladder irritation (4 patients), with no interruption of treatment. Due to the reduced number of patients with Hunner ulcer, we cannot establish whether the evolution of those cases was of a different type.

Summary data of these studies are presented in **Table 4**. Compared with the previous studies mentioned, the present research addresses in a more complex way the effects of HA in the evolution of both pathologies using several specific evaluation tools (VAS, quality of life), the evaluation of the specific symptoms (nocturia, bladder volume change) along with the fact that the evolution of patients after the end of treatment is followed for a longer period.

Our research is not intended as a comparative study nor a non-inferiority one, but followed the long-term evolution of patients with two different conditions, who can also benefit from this treatment. The two pathologies evolve with violent symptoms that do not decrease or disappear without treatment. Therefore, no control group could not be included in the study nor in any study of this type. On the other hand, our research focused primarily on assessing how long-term symptoms improved, and patients with such conditions could not be left untreated for 2 years (the duration of this research). Instillation treatment with HA was initially tested for BPS / IC patients, then expanded as a possible recommendation for those with urinary infections.

Women of any age are at increased risk of recurrent UTIs at an alarming rate. Treatment methods recommended and used around the world are still questionable when it comes to long-term effectiveness, as the clear mechanisms by which urinary tract infection appears are not yet elucidated. However, it is clear that we must first try to control the predisposing factors and call for patient behavioral change. Non-antimicrobial measures are important because they tend to reduce the use of antibiotic prophylaxis. In contrast, BPS/IC are a chronic and debilitating disease that clearly affect quality of life in all areas. In most studies, this condition is underdiagnosed due

to a lack of consensus on diagnosis, evaluation and treatment. Moreover, BPS/IC tend to be frustrating and difficult to manage, both for patients and doctors, creating a feeling of dissatisfaction with the quality of care.

One possible research limitation is the limited number of patients, however interstitial cystitis is a disease not very commonly diagnosed and treatments are not yet standardized. In this sense, most studies dealing with interstitial cystitis involve a low number of patients. We believe that, although our work is a multicenter study conducted in 3 large universities, the number of patients who could be evaluated and monitored is considered low.

5. Conclusions

HA instillation is an effective GAG substitution therapy in patients with recurrent UTIs and BPS/IC resistant to other types of therapy, an effect that persists over a non-negligible period of time post-treatment. Until the biggest problems with BPS/IC (controversies concerning definition, etiology, molecular mechanisms, pathology and prevalence) are resolved, our study demonstrates that intravesical HA instillations may be considered as an important component in the therapeutic strategy for optimal results in uncomplicated recurrent UTIs and BPS/IC over a long period. A longer patient observation period and enrollment in controlled, double-blind studies of several cases will be necessary to confirm the long-term efficacy of the product in these two clinically challenging pathologies that severely affect the patient's quality of life.

Ethical Statement

Each patient signed an informed consent form prior to inclusion in the study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki, and in

respect of ethical principles for medical research involving human subjects, approved by the Ethics Committees of the Emergency Clinical County Hospital of Brasov, of the Central Military Emergency University Hospital of Bucharest, and of the Emergency Clinical County Hospital of Targu Mures.

Disclosure Statement: The authors declare no conflict of interest.

Contribution: All authors had equal contribution to this paper.

Funding: This research received no external funding

References

Abdel-Daim MM, El-Tawil OS, Bungau SG, Atanasaov AG. Applications of Antioxidants in Metabolic Disorders and Degenerative Diseases: Mechanistic Approach. *Oxid Med Cell Longev* 2019; 2019:ID 4179676. <https://doi.org/10.1155/2019/4179676>

Ablove T, Patankar M, Seo S. Prevention of recurrent urinary tract infections by intravesical administration of heparin: a pilot study. *Ther Adv Urol* 2013; 5(6):303-9.

Abrams P, Hashim H, Tomson C, Macgowan A, Skews R, Warren K. The use of intravesical gentamicin to treat recurrent urinary tract infections in lower urinary tract dysfunction. *Neurourol Urodyn* 2017; 36(8):2109-2116.

Aydin A, Ahmed K, Zaman I, Khan MS, Dasgupta P. Recurrent urinary tract infections in women. *Int Urogynecol J* 2015; 26(6):795-804.

Beerepoot MA, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol* 2013; 190:1981-9.

Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, Nyberg L, Clemens JQ. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol* 2011; 186(2):540-4.

Bosch PC, Bosch DC. Treating interstitial cystitis/bladder pain syndrome as a chronic disease. *Rev Urol* 2014; 16(2):83-7.

Brewer ME, White WM, Klein FA, Klein LM, Waters WB. Validity of Pelvic Pain, Urgency, and Frequency questionnaire in patients with interstitial cystitis/painful bladder syndrome. *Urology* 2007; 70(4):646-9.

Bumbu A, Pasca B, Tit DM, Bungau S, Bumbu G, The effects of soy isoflavones and hormonal replacing therapy on the incidence and evolution of postmenopausal female urinary incontinence. *Farmacia* 2016; 64(3):419-22.

Burckhardt CS, Anderson KL. The Quality of Life Scale (QOLS): Reliability, Validity, and Utilization. *Health Qual Life Outcomes* 2003; 1:60.

Burckhardt CS, Jones KD. Adult measures of pain: The McGill Pain Questionnaire (MPQ), Rheumatoid Arthritis Pain Scale (RAPS), Short-Form McGill Pain Questionnaire (SF-MPQ), Verbal Descriptive Scale (VDS), Visual Analog Scale (VAS), and West Haven-Yale Multidisciplinary Pain Inventory (WHYMPI). *Arthritis Rheum* 2003; 49:S96-104.

Burkman RT. Chronic pelvic pain of bladder origin: epidemiology, pathogenesis and quality of life. *J Reprod Med* (2004) 49:225-9.

Chuang YC, Weng SF, Hsu YW, Huang CLC, Wu MP. Increased risks of healthcare-seeking behaviors of anxiety, depression and insomnia among patients with bladder pain syndrome/interstitial cystitis: a nationwide population-based study. *Int Urol Nephrol* 2015; 47:275.

Ciani O, Arendsen E, Romancik M, Constantini E, Di Blase M, Morgia G, et al. Intravesical administration of combined hyaluronic acid (HA) and chondroitin sulfate (CS) for the treatment of female recurrent urinary tract infections: a European multicentre nested case-control study. *BMJ Open* 2016; 6:e009669.

Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LMJr, McKinlay JB. BACH Survey Investigators. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. *J Urol* 2007; 177(4):1390-4.

Constantinides C, Manousakas T, Nikolopoulos P, Stanitsas A, Haritopoulos K, Giannopoulos A. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. *BJU Int* 2004; 93:1262-6.

Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; 18:340:c2096.

Cox L, He C, Bevins J, Clemens JQ, Stoffel JT, Cameron AP. Gentamicin bladder instillations decrease symptomatic urinary tract infections in neurogenic bladder patients on intermittent catheterization. *Can Urol Assoc J* 2017; 11(9):E350-E354.

Czaja CA, Hooton TM. Update on acute uncomplicated urinary tract infection in women. *Postgrad Med* 2006; 119:39-45.

Daha KL, Riedl CR, Lazar D, Simak R, Pflüger H. Effect of intravesical glycosaminoglycan substitution therapy on bladder pain syndrome/interstitial cystitis, bladder capacity and potassium sensitivity. *Scand J Urol* 2008; 8:369-72.

Daha LK, Riedl CR, Hohlbrugger G, Knoll M, Engelhardt PF, Pflüger H. Comparative assessment of maximal bladder capacity, 0.9% NaCl vs. 0.2 M KCl, for the diagnosis of interstitial cystitis: a prospective controlled study. *J Urol* 2003; 170:807-9.

Damiano R, Cicione A. The role of sodium hyaluronate and sodium chondroitin sulphate in the management of bladder disease. *Ther Adv Urol* 2011; 3(5):223-32.

Damiano R, Quarto G, Bava I, Ucciero G, De Domenico R, Palumbo MI, Autorino R. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. *Eur Urol* 2011; 59(4):645-51.

Dason S, Dason JT, Kapoor A. Guidelines for the diagnosis and management of recurrent urinary tract infection in women. *Can Urol Assoc J* 2011; 5(5):316-22.

Engeler D, Baranowski AP, Borovicka J, Cottrell AM, Dinis-Oliveira P, Elneil S, et al. EAU Guidelines on Chronic Pelvic Pain 2018. <http://uroweb.org/guideline/chronic-pelvic-pain/> (last accessed November 2018)

Epp A, Larochelle A. Recurrent Urinary Tract Infection. *J Obstetrics Gynaecol Can* 2010; 32(11):1082-90.

Fall M, Oberpenning F, Peecker R. Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? *Eur Urol* 2008; 54:65-75.

Foster RTSr. Uncomplicated urinary tract infections in women. *Obstet Gynecol Clin North Am* 2008; 35(2):235-48.

Foxman B, Gillespie B, Koopman J, Zhang L, Palin K, Tallman P, et al. Risk factors for second urinary tract infection among college women. *Am J Epidemiol* 2000; 151:1194-205.

Foxman B. Epidemiology of urinary tract infections: incidence, morbidity and economic costs. *Am J Med* 2002; 113(1A):5S–13S.

Gajewski JB, Al-Zahrani AA. The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int 2011; 107(8):1258-64.

Grigorescu B, Powers K, Lazarou G. Update on Urinary Tract Markers in Interstitial Cystitis/Bladder Pain Syndrome. Female Pelvic Med Reconstr Surg 2016; 22(1):16-23.

Gülpınar O, Haliloğlu AH, Gökce, Mİ, Arıkan N. Instillation of hyaluronic acid via electromotive drug administration can improve the efficacy of treatment in patients with interstitial cystitis/painful bladder syndrome: A randomized prospective study. Korean J Urol 2014; 55(5):354-9.

Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. World J Urol 1999; 17:415-20.

Han E, Nguyen L, Sirls L, Peters K. Current best practice management of interstitial cystitis/bladder pain syndrome. Therap Adv Urol 2018; 10(7):197-211.

Hanno P, Lin A, Nordling J, Nyberg L, van Ophoven A, Ueda T, Wein A. Bladder pain syndrome international consultation on incontinence. Neurourol Urodyn 2010; 29:191-8.

Hertting O, Holm A, Lüthje P, Brauner H, Dyrda R, Jonasson AF, et al. Vitamin D Induction of the Human Antimicrobial Peptide Cathelicidin in the Urinary Bladder. PLoS One 2010; 5(12):e15580.

Hooton TM. Recurrent urinary tract infection in women. Int J Antimicrob Agents 2001; 17:259-68.

Hurst RE, Roy JB, Min KW, Veltri RW, Marley G, Patton K, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology 1996; 48(5):817-21.

Iavazzo C, Athanasiou S, Pitsouni E, Falagas ME. Hyaluronic acid: an effective alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis. *Eur Urol* 2007; 51:1534-41.

Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain* 2003; 4:407-14.

Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986; 27:117-26.

Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012; CD001321.

Jhang JF, Kuo HC. Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention. *Ci Ji Yi Xue Za Zhi* 2017; 29(3):131-7.

Kallestrup EB, Jorgensen SS, Nordling J, Hald T. Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. *Scand J Urol Nephrol* 2005; 39(2):143-7.

Kaufman JE, Anderson K, Parsons CL. Inactivation of anti-adherence effect of bladder surface glycosaminoglycans as possible mechanism for carcinogenesis. *Urology* 1987; 30:255-8.

Lai MC, Kuo YC, Kuo HC. Intravesical hyaluronic acid for interstitial cystitis/painful bladder syndrome: a comparative randomized assessment of different regimens. *Int J Urol* 2013; 20(2):203-7.

Lazzeri M, Montorsi F. The therapeutic challenge of “chronic cystitis”: search well, work together, and gain results. *Eur Urol* 2011; 60:78-80.

Leppilahti M, Hellstrom P, Tammela TL. Effect of diagnostic hydrodistension and four intravesical Hyaluronic acid instillations on bladder ICAM-1 intensity and association of ICAM-1 intensity with clinical response in patients with interstitial cystitis. *Urology* 2002; 60:46-51.

Lipovac M, Kurz C, Reithmayr F, Verhoeven HC, Huber JC, Imhof M. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. *Int J Gynaecol Obstet* 2007; 96(3):192-5.

Logadottir YR, Ehren I, Fall M, Wiklund NP, Peeker R. Intravesical nitric oxide production discriminates between classic and nonulcer interstitial cystitis. *J Urol* 2004; 171(3):1148-51.

Magnus F, Oberpenning F, Peeker R. Treatment of Bladder Pain Syndrome / Interstitial Cystitis 2008: Can we make evidence-based decisions? *Eur Urol* 2008; 54(1):65-78.

Mullins C, Bavendam T, Kirkali Z, Kusek JW. Novel research approaches for interstitial cystitis/bladder pain syndrome: thinking beyond the bladder. *Transl Androl Urol* 2015; 4(5):524-33.

Nightingale G, Shehab Q, Kandiah C, Rush L, Rowe-Jones C, Philips CH. The effect of intravesical instillations with Hyaluronic Acid on sexual dysfunction in women with recurrent urinary tract infections (RUTI). *Eur J Obstetrics Gynecol Reproductive Biol* 2018; 221:105-8.

Oravisto KJ. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn* 1975; 64:75-7.

Parsons CL, Dell J, Stanford EJ, Bullen M, Kahn BS, Waxell T, Koziol JA. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002; 60(4):573-8.

Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol* 1991; 145(4):732-5.

Parsons CL. Potassium sensitivity test. *Tech Urol* 1996; 2:171-3.

Porru D, Campus G, Tudino D, Valdes E, Vespa A, Scarpa RM, Usai E. Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. *Urol Int* 1997; 59:26-9.

Pyo JS, Cho WJ. Systematic Review and Meta-Analysis of Intravesical Hyaluronic Acid and Hyaluronic Acid/Chondroitin Sulfate Instillation for Interstitial Cystitis/Painful Bladder Syndrome. *Cell Physiol Biochem* 2016; 39:1618-25.

Raymond I, Vasdev N, Ferguson J, Haskin M, Davis, L, Hasan, T S. The clinical effectiveness of intravesical sodium hyaluronate (cystistat®) in patients with interstitial cystitis/painful bladder syndrome and recurrent urinary tract infections. *Curr Urol* 2012; 6(2):93-8.

Riedl CR, Engelhardt PF, Daha KL, Morakis N, Pflüger H. Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. *Int Urogynecol J Pelvic Floor Dysfunct* 2008; 19(5):717-21.

Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med* 2002; 113(1A):14-9.

Rooney P, Srivastava A, Watson L, Quinlan LR, Pandit A. Hyaluronic acid decreases IL-6 and IL-8 secretion and permeability in an inflammatory model of interstitial cystitis. *Acta Biomater* 2015; 19:66-75.

Rovner E, Propert KJ, Bresinger C, Wein AJ, Foy M, Kirkemo A. et al. Treatment used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. *Urology* 2000; 56(6):940-5.

Sanchez-Freire V, Blanchard MG, Burkhard FC, Kessler TM, Kellenberger S, Monastyrskaya K. Acid-sensing channels in human bladder: expression, function and alterations during bladder pain syndrome. *J Urol* 2011; 186(4):1509-16.

Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. *J Infect Dis* 2000; 182:1177-82.

Sharifiaghdas F, Hamzehi Esfahani N. UP-2.62: Intravesical instillation of hyaluronic acid in the treatment of recurrent urinary tract infection in women. *Urology* 2010; 76(3):S102.

Smelov V, Naber K, Bjerklund Johansen TE. Improved Classification of Urinary Tract Infection: Future Considerations. *Euro Urol Supp* 2016; 15:71-80.

Smith AL, Brown J, Wyman JF, Berry A, Newman DK, Stapleton AE. Treatment and Prevention of Recurrent Lower Urinary Tract Infections in Women: A Rapid Review with Practice Recommendations. *J Urol* 2018; 5347(18):43408-8.

Stav K, Lindner A. Interstitial cystitis/painful bladder syndrome: a comprehensive review of the current literature. *Harefuah* 2011; 150:168-74.

Tit DM, Pallag A, Iovan C, Furu G, Furu C, Bungau S. Somatic-vegetative symptoms evolution in postmenopausal women treated with phytoestrogens and hormone replacement therapy. *Iran J Public Health* 2017; 46(11):1128-1134.

Vahlensieck W, Perepanova T, Bjerklund Johansen TE, Tenke P, Naber KG, Wagenlehner FME. Management of uncomplicated recurrent urinary tract infections. *Eur Urol Supp* 2016; 15(4):95-101.

Van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Kuroschi L, et al. Diagnostic Criteria, Classification, and Nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC Proposal. *Eur Urol* 2008; 53(1):60-7.

Vedanayagam M, Brewin J, Briggs K, Salahia G, Hammadeh M. The role of hyaluronic acid in the management of uncomplicated recurrent female urinary tract infections: Literature review and practical experience. *J Clin Urol* 2013; 6:243-8.

Vij M, Srikrishna S, Cardozo L. Interstitial cystitis: diagnosis and management. *Eur J Obstet Gynecol Reprod Biol* 2012; 161(1):1-7.

Wagenlehner FM, Vahlensieck W, Bauer HW, Weidner W, Piechota HJ, Naber, KG.
Prevention of recurrent urinary tract infections. *Minerva Urol Nefrol* 2013; 65:9-20.

Yeung AWK, Tzvetkov N, El-Tawil OS, Bungau SG, Abdel-Daim MM, Atanasov AG.
Antioxidants: scientific literature landscape analysis. *Oxid Med Cell Longev* 2019; 2019:ID
8278454. <https://doi.org/10.1155/2019/8278454>

Zaha DC, Bungau S, Aleya S, Tit DM, Vesa CM, Popa AR., Carmen P, Maghiar OA, Bratu
OG, Fura C, Moleriu RD, Petre I, Aleya L. What antibiotics for what pathogens? The
sensitivity spectrum of isolated strains in an intensive care unit. *Sci Total Environ* 2019; 687:118-
27. <https://doi.org/10.1016/j.scitotenv.2019.06.076>

Zhong YH, Fang Y, Zhou JZ, Tang Y, Gong SM, Ding Q. Effectiveness and safety of patient
initiated single-dose versus continuous low-dose antibiotic prophylaxis for recurrent urinary tract
infections in postmenopausal women: a randomized controlled study. *J Int Med Res* 2011;
39:2335-43.

List of figures

Figure 1. Symptomatic response and the evolution of symptomatology according to the scales in patients of Group I treated with HA instillation – 50 mL/ 40 mg in the case of recurrent urinary tract infections. (N/10 represents the average of the obtained values, having a range of possible values between 0 and 10, where 0 means the least (the minimum value) and 10 means the most (the maximum value).

Figure 2. Symptomatic response and the evolution of symptomatology according to the tested time points. (N/10 represents the average of the obtained values, having a range of possible values between 0 and 10, where 0 means the least (the minimum value) and 10 means the most (the maximum value).

Figure 3. Symptomatic response and the evolution of symptomatology according to the scales in patients of Group II (with PBS / IC) treated with HA instillation – 50 mL/ 40 mg for the case of painful bladder syndrome/ interstitial cystitis. (N/10 represents the average of the obtained values, having a range of possible values between 0 and 10, where 0 means the least (the minimum value) and 10 means the most (the maximum value).

Figure 4. The symptomatology evolution in four-time moments for the painful bladder syndrome/ interstitial cystitis. (N/10 represents the average of the obtained values, having a range of possible values between 0 and 10, where 0 means the least (the minimum value) and 10 means the most (the maximum value).

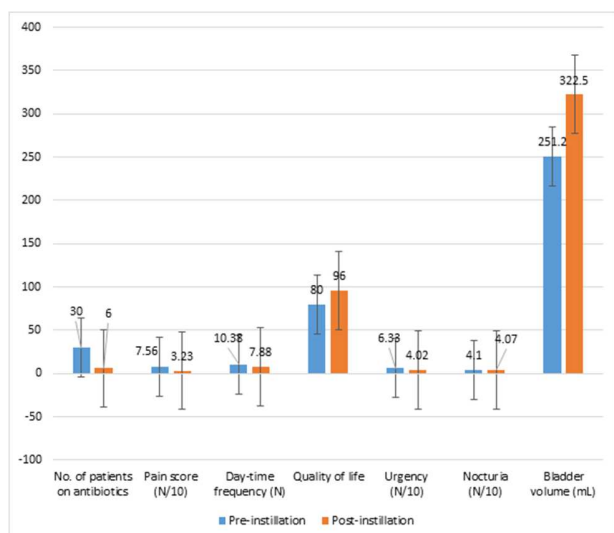


Figure 1.

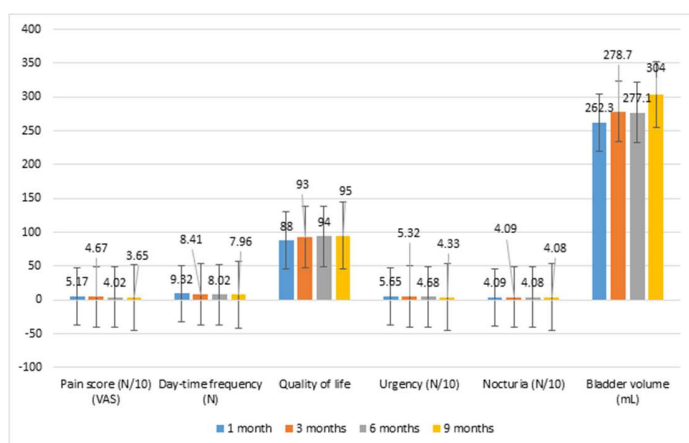


Figure 2.

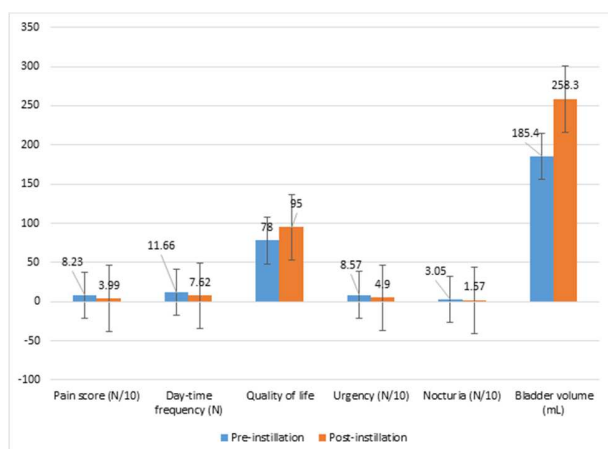


Figure 3.

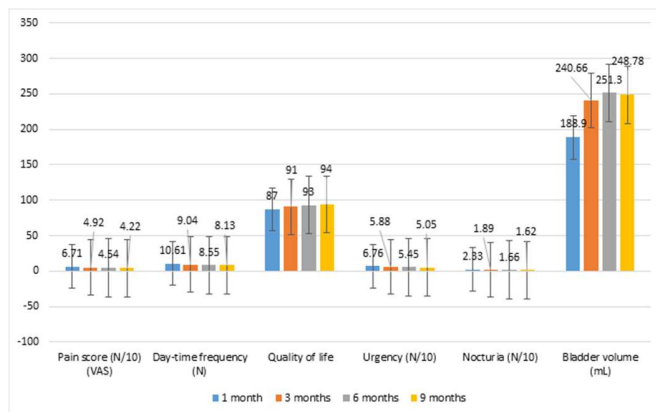


Figure 4.

Table 1. Most used instilling preparations for the treatment of BPS/IC commercialized in Europe

Intra-vesical agent/ active substance	Trade name	Composition
HA	Cystistat®	40 mg HMW-HA (0.08 %) / 50 mL
	Hyacyst®	40 / 120 mg HA (0.08 / 0.24 %) / 50 mL
	Uromac®	100 mg LMW HA (0.2 %) / 50 mL
CS	Gepan instill®	80 mg CS (0.2 %) / 40 mL
	Uracyst®	400 mg CS (2 %) / 20 mL
HA/CS	Ialuril®	800 mg LMW-HA (1.6 %)/1 g CS (2%)/50 mL
DMSO	Rimso-50®	27 g DMSO (5.4 %) / 50 mL
PPS	Cyst-u-ron®	300 mg PPS (1 %) / 30 mL

HA – sodium hyaluronate (hyaluronic acid), CS – Chondroitin sulphate, PPS – Pentosan polysulphate sodium, DMSO – Dimethyl sulfoxide, HMW – High molecular weight, LMW – Low molecular weight

Table 2. Pre-instillation parameters of patients (Mann Whitney U test)

Characteristics of patients	Group I (UTI)	Group II (BPS/IC)	p
Male:Female	0:30	0:24	-
Current age (years)	53.25±4.8	56.50±4.74	0.9633
Age at initial presentation (years)	45.28±4.72	52.00±4.52	0.4521
Urodynamic findings	DO (n=12), N (n=18)	DO (n=0), N (n=24)	-
Previous treatments			
Over-distention	3	12	-
Urethral dilatations	6	0	0.5745
Anticholinergics	3	3	1.0000
Botulinum toxin type A	3	3	0.3587
Patients on antibiotics, n	30 (100 %)	0 (0 %)	-
Pre-instillation bladder volume (mL)	251.2 ±34.5	185.4±15.55	-
Pre-instillation daytime frequency (N)	10.38±1.44	11.66±1.75	0.9840
Pre-instillation urgency (N/10)	6.33±0.81	8.57±0.61	0.9224
Pre-instillation pain score (N/10)	7.56±0.41	8.23±0.35	0.0568
Pre-instillation continence (N)	C (n=21), IC (n=9)	C (n=24), IC (n=0)	-
Pre-instillation nocturia (N)	4.1±0.56	3.05±0.52	0.7540
Pre-instillation QoL	80±11.2	78±12.4	0.6211

C – Continent; IC – Incontinent; DO – Detrusor Over-activity

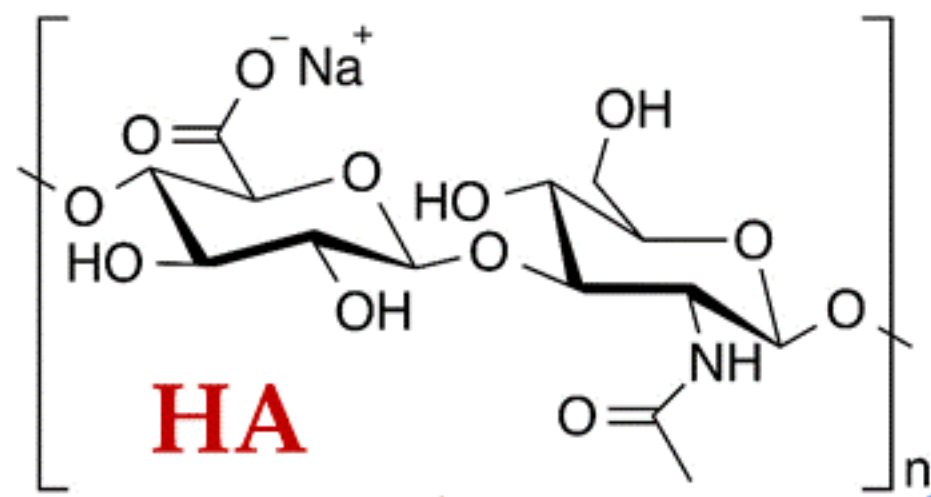
Table 3. Treatment characteristics

Followed parameters	Group I	Group II
Number of instillations	9.47±1.49	9.23±1.65
No. of patients having completed treatment	30	24
Duration of treatment (weeks)	23.4±5.92	21.9±8.79
Duration of follow-up from treatment (months)	19.9±5.98	15.23 ±6.88

Table 4. Summary of data retrieved from studies on intravesical HA for UTIs and IC/PBS

HA regime treatment; symptoms evaluated; no. of patients	Type of the study; follow-up time	Results	Reference
UTIs			
9 intravesical instillation over 6 months; UTI recurrence; n=20	Prospective 47.6 weeks compared with retrospective review of patient charts covering 36.2±6.2 weeks	<i>No. infections/year/ patient:</i> 4.99±0.92 to 0.56±0.82 (p<0.001). <i>Time to recurrence:</i> 178.3±25.5 days to 76.7±24.6 (p<0.001).	Lipovac et al., 2007
1/week intravesical instillation for 4 weeks, then 1/month for 4 months; UTI recurrence; n=40	Prospective follow-up of 12.4 months, compared with retrospective review of patient charts covering 15.8 months	<i>The mean (SD) rate of UTI/patient/year:</i> 4.3 (1.55) to 0.3 (0.55) (p<0.001). <i>The median time to recurrence</i> after HA: 498 days vs. 96 days beforehand (p<0.001). <i>Tolerability/adverse effects:</i> 9 patients reported mild bladder irritation, no patient interrupted the treatment.	Constantinides et al., 2004
Intravesical instillations 1/week for 1 month + once every others week for 2 months + 1/month for 5 months; urine cultures, UTI recurrence; n=30	Prospective study; follow-up 11 months after complete therapy	53 % <i>negative urine cultures</i> during the months of treatment phase. <i>Recurrence free</i> at the end of follow-up.	Sharifiaghdas and Hamzehi, 2010
9 intravesical instillations 23 weeks; Prophylactic antibiotic, VAS, day-time frequency, quality of life, urgency, nocturia, bladder volume change at 1, 3, 6 and 9 months; n=30 on prophylactic antibiotic therapy during the study period	Prospective study; follow-up 19.9±5.98 after complete therapy	<i>Prophylactic antibiotic:</i> 60 % complete response, interrupted antibiotic treatment; 20 % continued the low-dose prophylactic treatment. <i>Statistically significant improvements:</i> bladder pain, day-time frequency and quality of life. <i>Tolerability/adverse effects:</i> 6 patients reported bladder irritation with no interruption of treatment.	This study
IC/PBS			
1/week bladder instillations for 1 month + 1/month instillations for 2 months, patients were then offered further 1/month instillations; urinary frequency,	Prospective, unblinded, uncontrolled pilot study; subsequently evaluated after 3 years	<i>Mean decreases in nocturia and pain</i> of 40 % and 30 %, respectively. <i>Decrease in analgesic use.</i> <i>Tolerability/adverse effects:</i> tolerated by all patients.	Kallestrup et al. (2005)

use of analgesics and pain			
1/week instillations; VAS, quality of life; n=126	Prospective study; follow-up 5 years	<i>Symptoms improvement:</i> 85% reported (≥ 2 VAS units), VAS score of 8.5 decreased to 3.5 after therapy ($p < 0.0001$). <i>Quality of life:</i> 101 patients (84 %) significant improvement.	Riedl et al. (2008)
4 weekly intravesical instillations + 5 monthly instillations; Interstitial Cystitis Symptom and Problem Indexes, VAS, functional bladder capacity, frequency and nocturia in voiding diary, maximum flow rate, voided volume, postvoid residual volume, and quality of life, at 1, 3 and 6 months; n=30	Prospective, randomized study	<i>Statistically significant improvements:</i> Interstitial Cystitis Symptom Index, Interstitial Cystitis Problem Index and total score, VAS, functional bladder capacity, maximum flow rate, and Quality of Life Index, after 6 months in both groups.	Lai et al., 2013
9 intravesical HA instillations over nearly 22 weeks; VAS, day-time frequency, quality of life, urgency, nocturia, bladder volume change at 1, 3, 6 and 9 months; n=24	Prospective study; 15 months follow-up period	75 % of the patients demonstrated a complete response. <i>Statistically significant improvements:</i> pain score, life quality, urgency and nocturia.	This study



Group I
30 - UTIs

9.47 ± 1.49
instillations

After 20 months

Intra-vesical instillations
50 ml/40mg

9.23 ± 1.65
instillations

After 15 months

Group II
24 - BPS/IC

1. The Pelvic Pain and Urinary/Frequency Patient Symptom Scale questionnaires (PUF)
2. Visual analog scale (VAS)
3. The Quality of Life Scale (QoLS).

Pain score (N/10)

Day-time frequency (N)

Quality of life

Urgency (N/10)

Nocturia (N/10)

Bladder volume (mL)

Adverse effects

HA installation is an effective GAG substitution therapy in patients with recurrent UTIs and IC/BPS that were resistant to other types of therapy