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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

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28 Abstract

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

44

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

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51 **1. Introduction**

52 Uncomplicated recurrent UTIs are conditions just as incapacitating, expensive and frustrating, for
53 patients and medical staff alike. Almost 50% of all women will have UTIs during their lifetime
54 and for 33% this happens before the age of 24. Up to 35% of UTIs will repeat within 3-6 months
55 (Foxman, 2000; 2002). An uncomplicated UTI is defined as an infection that occurs in a healthy
56 person in the absence of structural or functional abnormalities of the urinary tract. Recurrent
57 uncomplicated UTI may be defined as 3 or more uncomplicated UTIs within 12 months (Hooton,
58 2001; Zhong et al., 2011). Also, the elevated incidence of this disease is associated with high cost
59 due to the repetitive use of many antibiotics and other treatments, as well as to multiple visits to
60 GPs, gynecologists or urologists (Foxman, 2002; Ronald 2002; Raymond et al., 2012).

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

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

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

80 Various techniques (instillations with chondroitin sulphate, heparin, pentosane polysulphate and
81 HA) for recovering the layer of GAG from the bladder mucosa level have been used with differing
82 results. Iavazzo et al. (2007) have shown a varied but positive response (30 to 73%) in patients
83 with BPS/IC when instillation with HA was used (Leppilahti et al., 2002; Iavazzo et al., 2007). In
84 patients with recurrent UTIs, Constantinides et al. (2004) obtained promising results with HA,
85 70% of patients being without recurrence at an average follow-up of 12.4 months. Treatment with
86 HA was first used with favorable results in patients with BPS/IC and the indication was later
87 extended to other conditions for which instillation was shown to be effective (recurrent UTIs or
88 radiation-induced cystitis). When trying to restore the protective barrier of the bladder by agents
89 with GAG substitution role, doctors encounter great difficulty as therapeutic agents are numerous,
90 with controversial results, and since adequate studies proving efficiency are lacking (Rovner et al.,
91 2000; Burkman, 2004). An optimal therapeutic regimen should be based on its ability to relieve
92 symptoms, improve patients' quality of life and diminish costs (Burkman, 2004). Products
93 available in Europe and currently used for instillations in the treatment of BPS/IC are listed in
94 **Table 1.**

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

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

110

111 **2. Material and methods**

112 **2.1. Study Design**

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

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

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

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

129 The exclusion criteria that our study considered, were:

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

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

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

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

146 In both groups, they were comparable in age and gender. All data were prospectively collected,

147 stored and processed; also, all steps necessary to establishing the correct diagnosis and potential

148 treatment were respected.

149 All the patients (in both groups) received intravesical HA instillations in doses of 50 mL / 40 mg

150 after the bladder was emptied. Subjects were advised to maintain the instilled substance in the

151 bladder for a minimum of 30 minutes, but preferably for 1-2 hours (following the product

152 guidelines). The procedure was initially carried out once a week over a period of 4 weeks and then

153 continued once every month (for 23.4 ± 5.92 weeks for Group I and 21.9 ± 8.79 weeks for Group II).

154 Group I (30 patients) received a low dose of an antibiotic, while Group II did not. Patients were

155 evaluated throughout the treatment period and post-instillation clinical parameters were monitored

156 at 15-20 months following treatment, with placement of therapeutic effects taking place over time.

157

158 **2.2. Clinical investigations**

159 All patients received pre- and post-treatment questionnaires ("The Pelvic Pain and
160 Urinary/Frequency Patient Symptom Scale Questionnaires" (PUF)) to assess their symptoms.

161 Urodynamic studies were performed in all patients in both groups in order to exclude any other

162 pathological cause of the symptoms. The PUF questionnaire, developed by C. Lowell Parsons, is

163 a rapid and informative diagnostic tool used to screen patients with chronic pelvic pain; it uses a

164 symptom score (which measures how often a patient experiences problems) and a bother score

165 (which notes the degree to which the symptoms bother the patient); the bother and symptom score

166 combine for a total PUF score. Scores range from 0 to 35; a score greater than 12 is considered
167 indicative of significant symptoms (Parsons et al., 2002; Brewer et al., 2007). Twelve patients
168 (40%) in Group I showed evidence of detrusor hyperactivity (OAB) in urodynamic tests, while the
169 remaining 18 patients had a normal urodynamic evaluation. All patients in Group II presented
170 urodynamic evaluations confirming the absence of OAB and additional parameters meeting the
171 criteria for inclusion of EAU diagnostic data.

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

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

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

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

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

205

206 **2.3. Statistical Analysis**

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

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

215

216 **2.4. Ethical Statement**

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

223

224 **3. Results**

225 **3.1. Patient base-line (pre-instillation) parameters**

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

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

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

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

237 **3.2. Patients' post-instillation parameters**

238 **3.2.1. Bladder pain**

239 Data was collected prospectively using the pre- and post-treatment questionnaires for pelvic pain,
240 with a symptom scale for urination and frequency as well as the VAS pain quizzes. For Group I
241 significant improvement in urinary bladder pain was observed at an average follow-up of 20
242 months. A statistically significant difference (Mann Whitney U test with $p=0.0007$) in pain
243 reduction on the VAS was seen from 7.56 ± 0.41 (pre-instillation) to 3.23 ± 0.69 (post-instillation).
244 Group II experienced a significant improvement in urinary bladder pain, reported a reduction in
245 pain-related symptoms on the VAS from 8.23 ± 0.35 to 3.99 ± 1.02 (Mann Whitney U test with
246 $p=0.0235$).

247 **3.2.2. Daytime urinary frequency**

248 For Group I significant improvement in daytime urinary frequency was observed, being reduced
249 from 10.38 ± 1.44 to 7.88 ± 1.41 (Mann Whitney U test with $p=0.0423$). In Group II, no statistically
250 significant change was found for daytime urinary frequency post-treatment, as a reduction was
251 reported from 11.66 ± 1.75 (pre-treatment) to 7.62 ± 0.88 (post-) (Mann Whitney U test with
252 $p=0.4013$).

253 **3.2.3. Quality of life**

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

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

258 **3.2.4. Urgency**

259 At the end of treatment, no statistically significant change was observed for urgency among Group
260 I patients: from 6.33 ± 0.81 (pre-treatment) to 4.02 ± 0.62 (post-treatment) (Mann Whitney U test
261 with $p=0.0693$). Group II, however, experienced a significant improvement in urgency, from
262 8.57 ± 0.61 to 4.9 ± 0.86 (Mann Whitney U test with $p=0.0252$).

263 **3.2.5. Nocturia**

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

269 **3.2.6. Bladder volume change**

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

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

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

292

293 **4. Discussion**

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

301 Current treatment options include the use of prophylactic antibiotics (Zaha et al., 2019), estrogen
302 replacement therapy in postmenopausal women (Epp and Larochelle, 2010; Smith et al., 2018;
303 Vahlensieck et al., 2016), cranberry juice (antioxidants) (Epp and Larochelle, 2010; Jepson et al.,
304 2012; Yeung et al., 2019) and lifestyle change (Epp and Larochelle, 2010; Jhang and Kuo, 2017)
305 which involve increased fluid consumption, more frequent emptying of the bladder, especially
306 before and after sexual activity, supplementary vitamin D (Hertting et al., 2010) plant disinfectants
307 and plant diuretics (Wagenlehner et al., 2013), acidification of urine (Vahlensieck et al., 2016),
308 immune active prophylaxis (47), prophylaxis with probiotics (*Lactobacillus* spp.) or D-mannose
309 (Vahlensieck et al., 2016). Antimicrobial prophylaxis should be considered just following the other
310 measures due to risk of adverse events and collateral damage. Antimicrobial prophylaxis can be
311 administered continuously (daily, weekly) for 3 or 6 or 12 months, or as a single post-coital dose
312 (nitrofurantoin, TMP, TMP/sulfamethoxazole, quinolone or other treatments) (Epp and
313 Larochelle, 2010; Vahlensieck et al., 2016; Zaha et al., 2019).

314 None of these options have been proven to produce long-term results. In addition, the most
315 effective treatment (antimicrobial treatment or prophylaxis) is associated with many adverse
316 events and side effects. Also, patient compliance with the treatment tends to decrease over time
317 (Epp and Larochelle, 2010; Vahlensieck et al., 2016; Wagenlehner et al., 2013; Beerepoot et al.,
318 2013). Among the general population, recurrent UTIs cause substantial costs, but on a personal
319 level this pathology is accompanied by considerable impact on the quality of life (Ciani et al.,
320 2016). In these cases, gentamicin instillation treatment is also recommended, with good though
321 questionable results (Ablove et al., 2013; Cox et al., 2017).

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

324 some authors have suggested the use of heparin instillation, with encouraging results in reducing
325 UTIs recurrences (Vij et al., 2012; Ablove et al., 2013). Also, combined HA and chondroitin
326 sulfate (CS) instillations appear to produce good results (Ciani et al., 2016; Damiano et al., 2011).
327 Some publications can be found in the literature on the intravesical use of HA for treatment of
328 recurrent UTIs. Glycosaminoglycan (GAG) deficiency in the urinary bladder epithelium is a
329 convincing factor in the etiology of recurrent UTIs (Rovner et al., 2000, Constantinides et al.,
330 2004; Damiano et al., 2011; Bumbu et al., 2016; Abdel-Daim et al., 2019).
331 Constantinides et al. (2004) conducted a pilot study on forty women, treated with HA instillations
332 for recurrent UTIs in 2004, obtaining no recurrence for five months, and 70% of patients had no
333 recurrence at a one-year follow-up visit. The average time to recurrence was approximately 17
334 months post-treatment, with high tolerability. Lipovac et al. (2007) practiced HA instillations for
335 more than 6 months (9 instillations) on 20 women with recurrent UTIs and showed a reduction in
336 the number of recurrences per person and per year, from statistically significant results, with an
337 increasing time to recurrence of up to 178 days after treatment. Some authors (Sharifiaghdas and
338 Hamzehi, 2010) conducted a study on thirty women with recurrent UTIs and reported good results,
339 with no recurrence 6 months after treatment. Other authors have also reported good results with
340 HA instillations, but those studies were conducted only on small groups of patients (Vedanayagam
341 et al., 2013, Nightingale et al., 2018).

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

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

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

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

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

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

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

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

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

402 Cystoscopic bladder biopsy studies revealed clear defects in the urothelial GAG layer, with
403 secondary occurrence of submucosal exposure to toxic substances in the urine, with cytotoxic
404 effect (Constantinides et al., 2004; Logadottir et al., 2004; Sanchez-Freire et al., 2011; Stav and
405 Lindner, 2011; Engeler et al., 2018). Not without significance is the fact that many studies show
406 that BPS/IC has a significant impact on quality of life, with consequent depression, anxiety,
407 impaired emotional functioning, insomnia and fatigue, including change of profession due to pain
408 (Bosch and Bosch, 2014; Chuang et al., 2015; Engeler et al., 2018). Different conservative
409 therapies have been suggested for BPS/IC: physiotherapy, behavioral modification, stress
410 reduction, dietary manipulation, all with different and inconstant results (van de Merwe et al.,
411 2008; Hanno et al., 2010; Engeler et al., 2018).

412 Types of surgical and medical treatment have been previously described in the literature for this
413 condition with varying results (Porru et al., 1997; Constantinides et al., 2004; Iavazzo et al., 2007;
414 Fall et al., 2008; Gajewski and Al-Zahrani, 2011; Engeler et al., 2018; Han et al., 2018). These
415 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

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

453 24 patients with BPS/IC were recruited for our study according to the EAU Diagnostic Criteria.
454 On average, each patient received 9 intravesical HA instillations over nearly 22 weeks. After a
455 follow-up period of 15 months, 75 % of these patients demonstrated a complete response. Six of
456 them (25 %) did not respond to this treatment and thus other therapeutic solutions were prescribed,
457 including radical surgery with a urinary derivation (n=3) and intravesical *Botulinum* toxin type A
458 (n=3).

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

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

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

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

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

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

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

493

494 **5. Conclusions**

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

504

505 **Ethical Statement**

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

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

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515

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732 **List of figures**

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

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

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

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

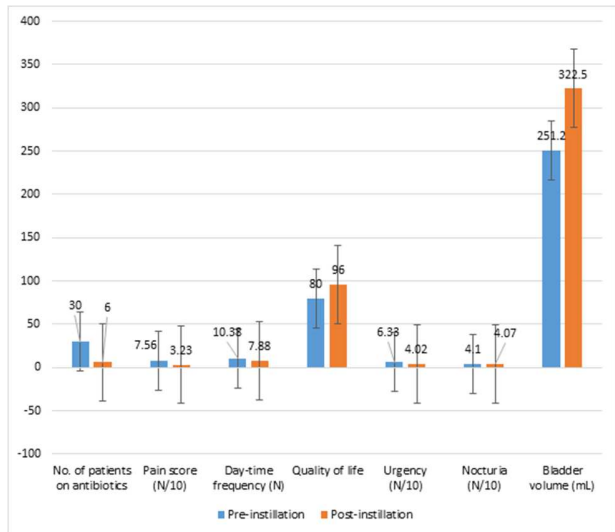


Figure 1.

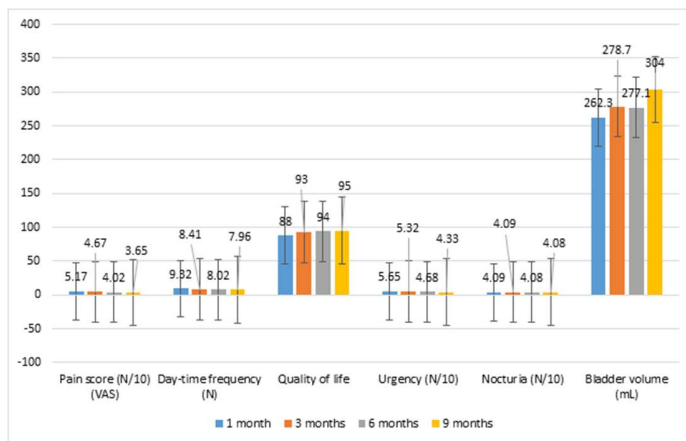


Figure 2.

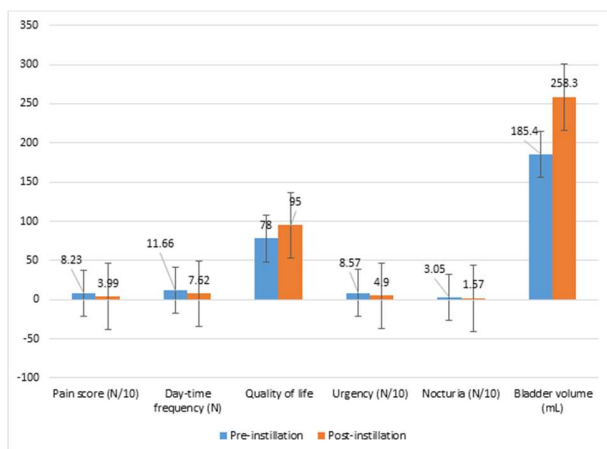


Figure 3.

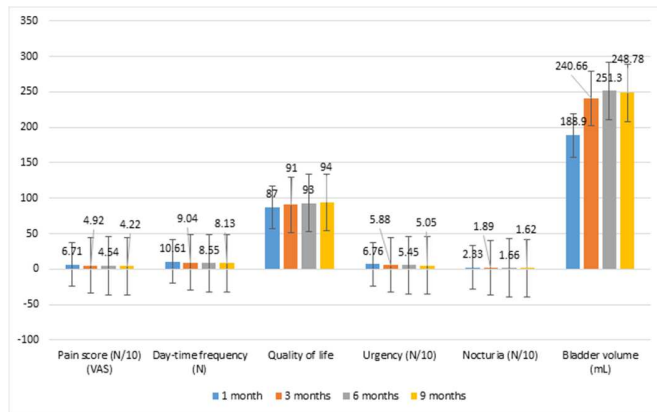


Figure 4.

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

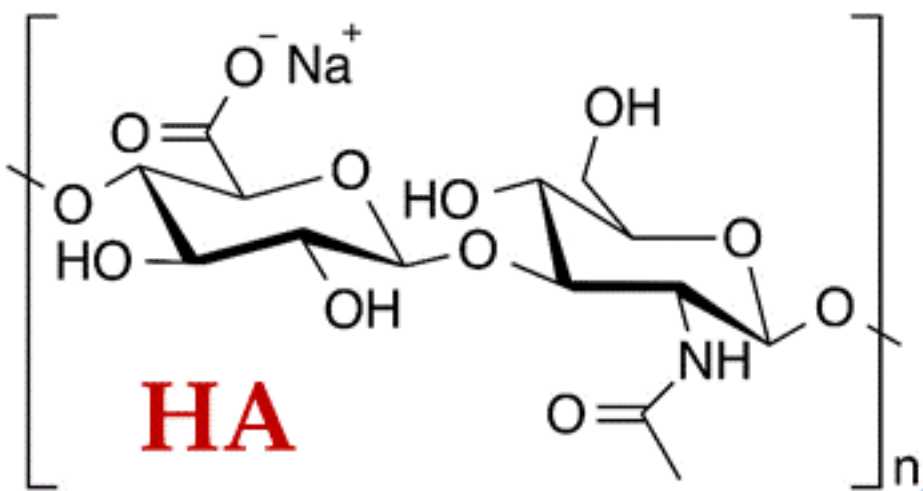
Table 3. Treatment characteristics

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: 4.99±0.92 to 0.56±0.82 (p<0.001). Time to recurrence: 178.3±25.5 days to 76.7±24.6 (p<0.001).</i>	<u>Lipovac et al., 2007</u>
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: 4.3 (1.55) to 0.3 (0.55) (p<0.001). The median time to recurrence after HA: 498 days vs. 96 days beforehand (p<0.001). Tolerability/adverse effects: 9 patients reported mild bladder irritation, no patient interrupted the treatment.</i>	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	<i>53 % negative urine cultures during the months of treatment phase. Recurrence free at the end of follow-up.</i>	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: 60 % complete response, interrupted antibiotic treatment; 20 % continued the low-dose prophylactic treatment. Statistically significant improvements: bladder pain, day-time frequency and quality of life. Tolerability/adverse effects: 6 patients reported bladder irritation with no interruption of treatment.</i>	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 of 40 % and 30 %, respectively. Decrease in analgesic use. Tolerability/adverse effects: tolerated by all patients.</i>	Kallestrup et al. (2005)

use of analgesics and pain			
1/week instillations; VAS, quality of life; n=126	Prospective study; follow-up 5 years	<p><i>Symptoms improvement:</i> 85% reported (≥ 2 VAS units), VAS score of 8.5 decreased to 3.5 after therapy ($p < 0.0001$).</p> <p><i>Quality of life:</i> 101 patients (84 %) significant improvement.</p>	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	<p><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.</p>	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	<p>75 % of the patients demonstrated a complete response.</p> <p><i>Statistically significant improvements:</i> pain score, life quality, urgency and nocturia.</p>	This study



54 patients

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