Ther Adv Urol
2016, Vol. 8(2) 91–99
DOI: 10.1177/1756287215621234

Managing chronic bladder diseases with the administration of exogenous glycosaminoglycans: an update on the evidence

Massimo Lazzeri, Rodolfo Hurle, Paolo Casale, NicolòMaria Buffi, Giovanni Lughezzani, Girolamo Fiorini, Roberto Peschechera, Luisa Pasini, Silvia Zandegiacomo, Alessio Benetti, Gianluigi Taverna, Giorgio Guazzoni and Guido Barbagli

***Abstract*:** Although the pathophysiology of acute chronic cystitis and other 'sensory' disorders, i.e. painful bladder syndrome (PBS) or interstitial cystitis (IC), often remains multifactorial, there is a wide consensus that such clinical conditions may arise from a primary defective urothelium lining or from damaged glycosaminoglycans (GAGs). A 'cascade' of events starting from GAG injury, which fails to heal, may lead to chronic bladder epithelial damage and neurogenic inflammation. To restore the GAG layer is becoming the main aim of new therapies for the treatment of chronic cystitis and PBS/IC. Preliminary experiences with GAG replenishment for different pathological conditions involving the lower urinary tract have been reported. There is a range of commercially available intravesical formulations of these components, alone or in combination. Literature evidence shows that exogenous intravesical hyaluronic acid markedly reduces recurrences of urinary tract infections (UTIs). Patients treated with exogenous GAGs have fewer UTI recurrences, a longer time to recurrence and a greater improvement in quality of life. Exogenous intravesical GAGs have been used for the treatment of PBS/IC. Despite the limitations of most of the studies, findings confirmed the role of combination therapy with hyaluronic acid and chondroitin sulfate as a safe and effective option for the treatment of PBS/IC. To prevent and/or treat radiotherapy and chemotherapy induced cystitis, GAG replenishment therapy has been used showing preliminary encouraging results. The safety profile of exogenous GAGs has been reported to be very favourable, without adverse events of particular significance.

Keywords: urothelium, cystitis, glycosaminoglycans, therapy

Correspondence to:
Massimo Lazzeri, MD, PhD
Department of Urology, Istituto Clinico Humanitas IRCCS, Clinical and Research Center, via Manzoni 56, 20089 Rozzano, MI, Italy
massimo.lazzeri@humanitas.it

Rodolfo Hurle, MD
Paolo Casale, MD
NicolòMaria Buffi, MD
Giovanni Lughezzani, MD
Girolamo Fiorini, MD
Roberto Peschechera, MD
Luisa Pasini, MD
Silvia Zandegiacomo, MD
Alessio Benetti, MD
Gianluigi Taverna, MD
Department of Urology, Istituto Clinico Humanitas IRCCS, Clinical and Research Center, Rozzano, MI, Italy

Giorgio Guazzoni
Department of Urology, Istituto Clinico Humanitas IRCCS, Clinical and Research Center, Humanitas University, Rozzano, MI, Italy

Guido Barbagli, MD
Centro Chirurgico Toscano, Arezzo, Italy

Introduction

One of the main purposes of physicians is to discover and deliver safe, effective and affordable treatments to patients based on their need. Acute and chronic cystitis due to bacteria, chemical or physical irritants which cause mucosal inflammation remain highly distressing conditions that urologists, gynaecologists and other caregivers find difficult to manage [Lazzeri and Montorsi, 2011]. Owing to different and often uncertain causes and aetiology, as in the case of painful bladder syndrome (PBS) or interstitial cystitis (IC), a clinical condition characterized by complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, most of the strategies used to alleviate symptoms have had disappointing results in the absence of proven urinary infection or other pathologies [Hanno *et al.* 2011].

Although the pathophysiology of acute chronic cystitis and other 'sensory' disorders, i.e. PBS/IC, often remains multifactorial, there is a wide consensus that such clinical conditions may arise from a primary defective urothelium lining or from a

damage of its glycosaminoglycan (GAG) component [Parsons, 2007]. A 'cascade' of events starting from GAG injury, which fails to heal, may lead to chronic bladder epithelial damage and neurogenic inflammation. Promptly restoring the GAG layer to prevent the cycle of inflammation and hypersensitization is one of the bases for the treatment of chronic cystitis and PBS/IC [Han *et al.* 2015].

We performed a systematic review using and matching different keywords: 'bladder', 'urothelium', 'glycosaminoglycans', 'functional disorders', 'cystitis', 'bladder pain', 'therapy', 'chronic bladder diseases', 'chemotherapy' and 'radiotherapy'. The research was performed using Medline (through PubMed), Embase, Web of Science and Cochrane Review databases; the search was developed from inception to 31 May 2015. In addition, we tried to obtain details of registered but not yet published trials. We selected and reported the most recent and updated evidence with GAGs replenishment for different pathological conditions involving the lower urinary tract. The aim of our paper was to provide the reader with the latest information about the clinical use of GAG therapy starting from the pathophysiological principles.

Pathophysiology of GAG damage

Different causes may be considered in the early stage of GAG injury. Autoimmune diseases, chronic bacterial infections, chemicals, anticancer drugs such as cyclophosphamide or Bacillus Calmette-Guérin (BCG) exposure, and radiation exposure can all result in urothelial GAG loss. Damaging this shielding layer results in the loss of 'watertight' function and allows both normal (i.e. H^+, K^+, Na^+, Cl^-) and abnormal constituents of urine (i.e. metabolites of cytotoxic drugs or toxic substances excreted into it) to come into direct contact with the subepithelial layers. This infiltration through the GAG barrier defect can cause subepithelial layer inflammation and delay or prevent the healing of the damaged bladder urothelial cells as well as the GAGs [Hurst *et al.* 1996]. The net result is the activation of a subset of unmyelinated C-fibres in the suburothelium [Maggi and Meli, 1988]. They are peptide-containing fibres (substance P, neurokinins A and B, calcitonine gene related peptide and bradykinin) and they result selectively sensitive to capsaicin, the pungent ingredient of red chilli [Maggi and Meli, 1988]. Although they serve as primary afferents, they may play an important role in the regulation of the lower urinary tract by an efferent function showing a characteristic 'double function' [Maggi and Meli, 1988]. The afferent function, mediated by the release of neuropeptides from their central endings, is involved in the regulation of micturition reflex, pain sensation and activation of visceral reflex. The efferent function, due to the release of substance P, calcitonin gene related peptide and tachykinins from peripheral endings, regulates the smooth muscle contraction, immunocell migration, mast cells degranulation and neurogenic inflammation. They are actively involved in the cotransmission phenomenon (axons release more than one transmitter for each action potential), in neuromodulation (locally released agents may modulate the amount of neurotransmitters released prejunctionally) and in nervous system plasticity during development, aging, chronic inflammation and spinal cord injury (neuroplasticity) [Lazzeri, 2009]. Evidence supports their role in bladder chronic inflammation [Sculptoreanu *et al.* 2005]. The activation of sensory fibres due to the defect of GAGs, which would allow the back flow of irritants in the submucosa, is involved in the increase of frequency in chronically inflamed bladders. Capsazepine, which is a selective capsaicin antagonist, decreased the frequency of reflex contractions in cyclophosphamide inflamed rat urinary bladders [Dinis *et al.* 2004].

When the GAG defect persists or its healing process fails, chronic stimulation of suburothelial tissues may result in visceral hypersensitivity of bladder C-fibres nociceptors [Doyle *et al.* 1997]. Clinically, the neuronal hypersensitivity, the exaggerated perception to normal stimuli, leads to allodynia, the perception of nociceptive stimulation which occurs for stimuli that would usually evoke an innocuous sensation (i.e. pain during bladder filling) and to hyperalgesia: exaggerated pain sensation to a stimulation which is normally mildly noxious (i.e. high pain intensity for mild inflammation). Under these conditions, the central nervous system receives an increased afferent barrage from peripheral bladder nervous endings. This barrage, in turn, triggers central mechanisms that amplify and sustain the effect of the sensory nerve peripheral input, leading to molecular changes in the peripheral organs and in the central nervous system [Doyle *et al.* 1997]. It has been observed that changes in density of neuropeptides in sensory nerves develop over a period of 5–7 days and that they are preceded by changes in level of activation of transcription factors.

Changes of the level of transcription factor c-jun and Oct-2 were found early in the inflammation conditions and the consequences were an increase of neuronal growth [Doyle *et al.* 1997]. The nuclear factor κB (NF-κB), known to exist in an inducible form in a wide range of eukaryotic cells, is activated by inflammatory mediators and has been thought to be responsible for hypersensibility. The direct consequence of all these changes is an increase of neuropeptide synthesis and their release at the level of synapses. Clinically the increase of release of neuropeptides at the level of bladder will produce chronic pain, an increase of frequency, nocturia and urgency, and sustain a neurogenic inflammation, while at the level of central nervous system it will lead to selective expression of genes (i.e. c-fos) [Doyle *et al.* 1997]. A nerve sprouting will be observed in the grey matter of the dorsal horn of the spinal cord with an increase in craniocaudal and latero-lateral synapses resulting in hypersensibility [Carter *et al.* 1996]. According to these theories, the early repair of the GAG layer by exogenous hyaluronic acid (HA) and chondroitin sulfate (CS), both mucopolysaccharides which act by different mechanisms of action, inhibition of adherence of immune complexes to polymorphonuclear cells, inhibition of leukocyte migration and aggregation, regulation of fibroblast and endothelial cell proliferation, and enhancement of connective tissue healing [Iavazzo *et al.* 2007], might avoid chronic evolution of bladder inflammation.

Clinical evidence

Urinary tract infections

Almost 50% of women will experience at least one urinary tract infection (UTI) in their lifetime and, in 20–50% of these, the episode is followed by a second infection within 6 months [Laupland *et al.* 2007]. In the US, up to 15% of women develop UTIs each year, and 1 in 4 of those will have ⩾1 recurrences. This condition is not, however, restricted to women, and it is estimated that the annual incidence of UTIs in males aged 17–79 years in the US is 2.2% [Guay, 2008]. The symptoms of UTIs, particularly when recurrent, impact on quality of life and productivity, affecting physical and emotional functioning, vitality, sexual and social functioning, and general health perceptions [Foxman, 2002].

Eradication of the infection has been the aim of current management strategies. Continuous or patient-initiated antimicrobial therapy is the current standard management practice for the treatment of acute UTIs and the prophylaxis of recurrent UTIs [European Association of Urology, 2015]. Agents include trimethoprim with or without sulfamethoxide, nitrofurantoin, cefaclor, cephalexin, norfloxacin, ciprofloxacin and fosfomycin. The disadvantages of this choice of treatment include the adverse effects associated with the antimicrobial agents and the increasing drug resistance [Sorlozano *et al.* 2014].

Despite our broad array of very successful antimicrobial agents, UTIs remain a complex clinical condition. These may present different severities, be acute or chronic, symptomatic or asymptomatic, be community or nosocomial acquired, and be sporadic or recurrent. The relationship between the host and uropathogens is pivotal in the initiation, development, maintenance and recurrence of UTIs, and an understanding of this interaction is therefore important in the prevention of the chronic or recurrent UTIs. On the uropathogen side, the virulence of the interaction between the uropathogen and host is determined by one or more factors, including adhesins, siderophore systems, biofilms, toxins, autotransporters, lipopolysaccharides, capsules, flagella or fimbria, metabolic traits, urease and pathogenomics. On the host side, the defence mechanisms contributing to the bladder's natural resistance to bacterial colonization include the regular flushing of the bladder, and the pH and osmolality of urine, which does not support bacterial growth. In addition, urothelial GAGs also play an important role in fending off infection, by virtue of them forming a physical barrier. This class of polysaccharides has hydrorepellant properties, making the inner bladder wall impervious to urine contents. Key components of this GAG layer are HA and CS.

There is a range of commercially available intravesical formulations of these components, alone or in combination. There are formulations containing a low concentration of HA (0.08%), a low concentration of CS (0.2%) or a high concentration of CS (2%). Exogenous GAGs, especially in the combination of HA and CS [Ialuril®, Institute Biochimique (IBSA)], were originally investigated for efficacy in patients with PBS/IC who had not benefited from other therapies [Cervigni *et al.* 2008], but more recent studies showed its efficacy in the prevention of recurrent UTIs in patients who had at least three episodes of

bacterial cystitis in the previous year [Damiano *et al.* 2011].

Earlier observational studies showing that exogenous intravesical HA markedly reduced recurrences of UTIs [Constantinides *et al.* 2004; Lipovac *et al.* 2007] were followed by a prospective study of the combination of HA and CS in patients with recurrent UTIs [Damiano *et al.* 2011]. This randomized, double-blind, placebo-controlled trial of Ialuril (four instillations at weekly intervals, then five instillations at monthly intervals) monitored 28 patients randomized to Ialuril and 29 patients randomized to placebo for 12 months. Patients treated with active drug had fewer UTI recurrences, a longer time to recurrence and a greater improvement in quality of life than patients in the placebo group. They experienced fewer UTI episodes and a longer mean time to recurrence than patients receiving placebo (87% *versus* 10% and 185 *versus* 53 days; $p < 0.05$ for both); the total number of UTIs experienced at 6 and 12 months was also significantly less ($p < 0.05$) in the Ialuril group. Symptoms (according to the pelvic pain, urgency and frequency score) improved significantly and quality of life was improved as well through 12 months ($p < 0.001$).

De Vita and colleagues compared exogenous intravesical GAGs to antibiotic prophylaxis for recurrent UTIs in 28 women; the intravesical treatment significantly reduced the recurrence of UTIs and improved urinary symptoms, quality of life and cystometric capacity at 12 months follow up [De Vita *et al.* 2010]. Results in the GAGs (Ialuril) and antibiotic groups were: number of recurrences (1 *versus* 2.3; $p = 0.02$), mean 3-day voiding (17.8 *versus* 24.2; $p = 0.04$), symptoms according to visual analogue scale score (pain 1.6 *versus* 7.8; $p < 0.001$), Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) score (11.2 *versus* 19.6; $p < 0.001$), King's Health Questionnaire (KHQ) score (18.4 *versus* 47.3; $p < 0.001$) and maximum cystometric capacity (380 *versus* 229 ml; $p < 0.001$). As in the Damiano study, tolerability of the Ialuril formulation was good, with no serious adverse events reported. Recently Cicione and colleagues [Cicione *et al.* 2014] assessed the effectiveness of intravesical instillation of HA and CS as a nonantibiotic treatment option for the prophylaxis of recurrent UTIs in female patients at seven European institutions. They used intravesical instillations of 50 ml HA 1.6% and CS 2% solution in 157 women with recurrent UTIs. UTI episodes decreased from 4.13 ± 1.14 to 0.44 ± 0.50 ($p = 0.01$) at 12 months, while recurrent UTI time increased from 94.8 ± 25.1 days to 178.4 ± 37.3 days ($p = 0.01$) at 12 months. An improvement in symptoms and quality of life was achieved.

In conclusion, restoring GAG bladder layer therapy seems to be a promising nonantibiotic therapy to prevent recurrent UTIs.

Painful bladder syndrome/interstitial cystitis

To improve the integrity and function of the bladder lining, exogenous intravesical GAG replacement therapies are one of the treatment options for patients with PBS/IC, generally refractory to conventional therapy [European Association of Urology, 2015]. There are four different commercially available products for GAG replenishment including CS, heparin, HA and pentosanpolysulfate. Each product has different concentrations and dosage formulations. A combination of CS and HA is the latest commercially available product. Exogenous intravesical HA was the first GAG used for the treatment of PBS/IC, followed by other different commercially available products for GAG replenishment including CS, heparin, HA and pentosanpolysulfate. The combination of CS and HA (Ialuril, IBSA) is the latest commercially available product.

Morales and colleagues found a complete or partial response rate of 71% for up to 1 year [Morales *et al.* 1996]. Recently Engelhardt and colleagues observed a 50% complete bladder symptom remission after intravesical HA. Those patients who responded did not use additional therapy during the 5-year follow up; 41.7% with symptom recurrence improved with HA maintenance [Engelhardt *et al.* 2011]. Hanno and colleagues reached a different conclusion [Hanno *et al.* 2005]. They carried out a double-blind, placebo-controlled, multicentre clinical study of different HA preparations (40 or 200 mg/cc) and did not find any significant efficacy of sodium hyaluronate compared with placebo.

Steeinhoff and colleagues investigated the exogenous CS therapy efficiency through an open-label 12-month study. They found a response rate for symptom improvement of 67% in 18 patients with 40 ml instillations of CS 0.2% weekly for 4 weeks and then monthly for 12 months [Steinhoff *et al.* 2002]. A recently published randomized, controlled trial (RCT) failed to show superiority

of CS 2.0% over control after 6 weeks of treatment [Nickel *et al.* 2010].

Porru and colleagues investigated the efficiency of intravesical CS/HA combination in 20 PBS/IC patients. Visual analogue scale (VAS) for pain and urgency, number of void per day, mean voiding volume, Interstitial Cystitis Symptom Index (ICSI) and PUF questionnaire improved compared with baseline [Porru *et al.* 2012]. Cervigni and colleagues seemed to confirm such results. They reported the long-term results of intravesical CS/HA therapy in 12 patients and showed the sustained efficiency for 3 years in terms of mean number of voids per day and mean volume per void with the confirmation of quality of life assessments [Cervigni *et al.* 2012]. The same group confirmed such results in 2014 [Cervigni *et al.* 2014]. In this study 73 patients were treated with Ialuril and 35 with RIMSO-50®. At baseline, mean pain VAS scores of 65.88 [standard deviation (SD) 20.93] and 64.14 (SD 20.66) were reported in the Ialuril and the RIMSO-50 groups, respectively. At the end-of-treatment visit, the response to treatment in terms of pain decrease from baseline was statistically significant in both groups, with a VAS score reduction of -39.53 (SD 24.58) for Ialuril and of -31.89 (SD 26.22) for RIMSO-50. For the 59 patients in the Ialuril and the 31 patients in the RIMSO-50 group completing the follow-up period, the mean VAS reduction was -43.71 (SD 28.56) and -33.65 (SD 31.31), respectively. The results from voiding diaries and the questionnaire scores were consistent with pain reduction. There was a higher proportion of patients with adverse events in the RIMSO-50 [28.6%; 95% confidence intervals (CI) 13.61–43.45) than in the Ialuril (15%; 95% CI 6.86–23.27) group. A case of strangury and a case of sovrapubic pain, both treatment-related, led to withdrawal of two patients, one per group.

Despite the limitations of most of those studies, the findings confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment for PBS/IC.

Chemotherapy and radiotherapy induced cystitis

Cystitis can be induced by both radiotherapy and chemotherapy, and can be either acute or chronic [Payne *et al.* 2013]. The condition often results in storage type lower urinary tract symptoms and haematuria. It is generally thought that damage to the GAG layer coating the urothelium is the initial trigger for the development of cystitis. In order to prevent and/or treat such conditions, GAG replenishment therapy with CS, heparin, HA and a new combination of CS and HA (Ialuril, IBSA) have been used.

Shao and colleagues randomized 36 patients undergoing radiotherapy for gynaecological malignancies to receive either HA or hyperbaric oxygen therapy (HBOT) [Shao *et al.* 2012]. They found no significant differences between the two groups in terms of haematuria, voiding frequency or VAS pain at 6, 12 and 18 months after treatment, except for a decreased frequency of voiding at 12 months in the HA group.

Sommariva and colleagues studied the effects of intravesical HA + CS in patients with symptomatic late radiation tissue cystitis [Sommariva *et al.* 2014]. In this 12-month, prospective, longitudinal, nonrandomized, investigative pilot study, patients with severe haematuria received daily instillations 5 days/week in the first month, 3 days/week in the second month, 2 days/week in the third month, once weekly in months 4–6, every 2 weeks in months 7–8, every 3 weeks in months 9–10 and monthly/bimonthly for 1 year. Patients without or with occasional haematuria received instillations 3 days/week in the first month, 2 days/week in the second month, 1 day/week in months 3–4, every 2 weeks in months 5–6, every 3 weeks in months 7–8 and monthly/bimonthly for 1 year. A total of 32 patients were enrolled. The authors found interesting results. Starting from a mean baseline of 66.9 ml, bladder capacity significantly increased to 101.9 ml at 3 months and to 174.4 ml at 12 months ($p < 0.05$ for both *versus* baseline). Voiding frequency also significantly decreased from 14.6 per day at baseline to 10.5 per day at month 3 and 8.8 per day at month 12 ($p < 0.001$ for both *versus* baseline). Significant increases were observed after 3 and 12 months for the quality of life as measured by the EQ-5D™ and EQ-5D VAS. However, the fact that the Sommariva study is not a RCT and does not include a control group limits clear conclusions. Other factors, such as a more intense schedule treatment, a prevalence of male population, different types of tumour than those investigated in previous available studies, require further investigations to better define the feasibility of a tailored-made therapy.

Giannessi and colleagues investigated a group of patients with cystitis and nocturia related to post

Table 1. Clinical evidence of exogenous glycosaminoglycans treatment for cystitis.

Condition	Number of patients (treatment)	Reference
UTIs	157 (HA/CS)	Cicione *et al*. [2014]
UTIs	23(Fosfomycin)	Torella *et al*. [2013]
	22 (HA/CS)	
	24 (Ialuril® + Fosfomycin)	
UTIs	14 (HA/CS) *versus* 14 (control)	De Vita and Giordano [2012]
UTIs	28 (HA/CS) *versus* 28 (placebo)	Damiano *et al*. [2011]
PBS/IC	19 (HA/CS)	Morelli *et al*. [2015]
PBS/IC	20 (HA/CS)	Giberti *et al*. [2013]
PBS/IC and UTIs	12 UTIs + 9 IC/PBS (HA/CS)	Costantini *et al*.·[2013] .
PBS/IC	22 (HA/CS)	Porru *et al*. [2012]
PBS/IC	12 (HA/CS)	Cervigni *et al*. [2012]
PBS/ICand UTIs	13 UTIs + 17 IC/PBS (HA/CS)	Bassi *et al*. [2011]
PBS/IC	23 (HA/CS)	Porru, *et al*. [2008]
PBS/IC	23 (HA/CS)	Cervigni *et al*. [2008]
Cystitis after external radiotherapy for prostate cancer (PCa)	23 (HA/CS)	Gacci *et al*. [2015
Late radiation tissue cystitis (LRTC)	27 (HA/CS)	Sommariva *et al.* [2014]
PBS/IC	73 IC/PBS (HA/CS) *versus* 35 IC/PBS (DMSO)	Cervigni *et al*. [2014]
Recurrent bacterial cystitis	99 patients antibiotics *versus* 112 patients (HA/CS)	Adile *et al*. [2014]
Mitomycin, epirubicin or BCG-induced chemical cystitis	55 asymptomatic patients (HA/CS)	Serretta [2014]
	10 volunteers control	
PBS/IC	73 IC/PBS (HA/CS) *versus* 35 IC/PBS (DMSO)	Cervigni *et al*. [2014]
PBS due to pelvic irradiation for locally advanced prostate cancer	23 radiation cystitis (HA/CS)	Giannessi *et al*. [2014]
BCG-induced chemical cystitis	15 chemical cystitis (HA/CS)	Imperatore *et al*. [2014]
Chronic cystitis and PBS/IC	15 chronic cystitis + 16 IC/PBS (HA/CS)	Yoon *et al*. [2013]
BCG-induced chemical cystitis	24 (HA/CS)	Li Marzi *et al*. [2013]
BCG-induced chemical cystitis	15 (HA/CS)	Creta *et al*. [2012]

BCG, Bacillus Calmette-Guérin; CS, chondroitin sulfate; HA, hyaluronic acid; IC, interstitial cystitis; PBS, painful bladder syndrome; UTI, urinary tract infection.

radiation bladder pain [Giannessi *et al.* 2014]. This study evaluated the impact of HA + CS on symptoms and bother related to nocturia in men with PBS. The authors concluded that HA + CS was effective in reducing nocturia and related bother after radiotherapy. Gacci and colleagues confirmed such results [Gacci *et al.* 2015]. Although bladder instillation treatment with a combination of HA and CS can be considered effective in reducing nocturnal voiding frequency in men with post radiation bladder pain for prostate cancer (PCa), RCTs with sham treatment are needed to extend and validate results.

BCG-induced chemical cystitis unresponsive to conventional therapies represents a considerable challenge for clinicians. While BCG is considered to be an effective treatment to reduce the recurrence and progression of nonmuscle invasive bladder cancer (NMIBC), it is indeed associated with local treatment-related side effects that can lead to discontinuation or interruption.

Imperatore and colleagues investigated treatment of BCG-induced chemical cystitis unresponsive to traditional treatments with intravesical administration of HA + CS [Imperatore *et al.* 2014]. At

all follow-up times, significant improvements were seen in VAS scores for pain and urgency, voids per 24 hours, and urine volume per void (Table 1). Significant improvements were observed throughout the 12-week study period. These authors concluded that intravesical instillation of HA + CS is an efficacious strategy for refractory BCG-induced chemical cystitis with results that appear to be long-lasting.

Finally Topazio and colleagues investigated if sequential administration of HA could reduce the side effects related to BCG [Topazio *et al.* 2014] A total of 30 consecutive subjects undergoing BCG intravesical administration for high risk NMIBC were randomized to receive either BCG alone or BCG and HA. The mean VAS for pain was significantly lower in the group receiving the combination of BCG and HA. The International Prostate Symptom Score (IPSS) and the number of daily micturitions were all significantly lower in the group receiving BCG and HA

Conclusion

Robust evidence indicates that a defective urothelial barrier may underlie or be involved in the pathogenesis of several chronic bladder conditions such as PBS/IC, recurrent UTIs, and chemical and radiation cystitis. These different clinical entities, which in the past were considered distinct diseases, can now be viewed as diseases caused as a result of the dysfunction of a common physiological element, the urothelium and associated GAG lining.

This renewed approach to looking at the pathophysiology of these GAG disorders will allow the development of more effective treatments for these debilitating and sometimes chronic diseases. Preliminary studies of the intravesical instillation of a combined solution containing a high concentration of HA and CS as GAG replacement therapy suggest that this formulation has efficacy potential in both UTIs and PBS/IC. Importantly, the safety profile of this combination has been reported to be very favourable, without adverse events of particular significance. New emerging oral formulations could be a noninvasive and complementary approach, although no evidence yet exists.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

Adile, B., Calagna, G., Adile, G., Granese, R., Polito, S., Saitta, S. *et al.* (2014) Usefull of intravesical instillation of hyaluronic acid and chondroitin sulphate in preventing recurrent bacterial cystitis. ICS 2014, 20–24 October 2014, Rio de Janeiro, abstract 577.

Bassi, P., Costantini, E., Foley, S. and Palea, S. (2011) Glycosaminoglycan therapy for bladder diseases: emerging new treatments review article. *Eur Urol* 10: 451–459.

Carter, B., Kaltschmidt, C., Kaltschmidt, B., Offenhäuser, N., Böhm-Matthaei, R., Baeuerle, P. *et al.* (1996) Selective activation of NF-kappa B by nerve growth factor through the neurotrophin receptor p75. *Science* 272: 542–545.

Cervigni, M., Natale, F., Nasta, L. and Mako, A. (2012) Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: Long-term treatment results. *Int Urogynecol J* 23: 1187–1192.

Cervigni, M., Natale, F., Nasta, L., Padoa, A., Voi, R. and Porru, D. (2008) A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct* 19: 943–947.

Cervigni, M., Sommariva, M., Porru, D., Ostardo, E., Tenaglia, R., Giammò, A. *et al.* (2014) A randomized, open-label, multicentre study of efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate (HA 1.6% and CS 2%) *versus* dimethyl sulfoxide (DMSO 50%) in women with bladder pain syndrome/interstitial cystitis (BPS/IC). *Eur Urol* 13: e464.

Cicione, A., Cantiello, F., Ucciero, G., Salonia, A., Torella, M., De Sio, M. *et al.* (2014) Intravesical treatment with highly-concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: results from a multicentre survey. *Can Urol Assoc J* 8: E721–E727.

Constantinides, C., Manousakas, T., Nikolopoulos, P., Stanitsas, A., Haritopoulos, K. and Giannopoulos, A. (2004) Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. *BJU Int* 93: 1262–1266.

Costantini, E., Lazzeri, M., Pistolesi, D., Del Zingaro, M., Frumenzio, E., Boni, A. *et al.* (2013) Morphological changes of bladder mucosa in patients

who underwent instillation with combined sodium hyaluronic acid-chondroitin sulphate (Ialuril®). *Urol Int* 91: 81–88.

Creta, M., Di Meo, S., Buonopane, R. and Imperatore, V. (2012) Intravesical administration of hyaluronic acid and chondroitin sulphate for bacillus Calmette-Guerin induced chemical cystitis. 85th Italian Society of Urology Congress, 21–24 October 2012, Venice, Italy: poster P164.

Damiano, R., Quarto, G., Bava, I., Ucciero, G., De Domenico, R., Palumbo, M. *et al.* (2011) Autorino, R. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. *Eur Urol* 59: 645–651.

De Vita, D. and Giordano, S. (2012) Effectiveness of intravesical hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: a randomized study. *Int Urogynecol J* 23: 1707–1713.

De Vita, D., Giordano, S. and Coppola, E. (2010) Prospective observational study of intravesical sodium hyaluronate and chondroitin sulfate in women with chronic cystitis, recurrent bacterial cystitis: preliminary data. 86th SIGO Congress, 14–17 November 2010, Milan, Italy.

Dinis, P., Charrua, A., Avelino, A., Yaqoob, M., Bevan, S., Nagy, I. *et al.* (2004) Anandamide-evoked activation of vanilloid receptor 1 contributes to the development of bladder hyperreflexia and nociceptive transmission to spinal dorsal horn neurons in cystitis. *J Neurosci* 24: 11253–11263.

Doyle, C., Palmer, J., Munglani, R. and Hunt, S. (1997) Molecular consequences of noxious stimulation. In: Borsook, D. (ed.), *Molecular Neurobiology of Pain*, Progress in Pain Research and management, Vol. 9. Seattle, WA: IASP Press, pp. 145–170.

Engelhardt, P., Morakis, N., Daha, L., Esterbauer, B. and Riedl, C. (2011) Long-term results of intravesicalhyaluronan therapy in bladder pain syndrome/interstitial cystitis. *Int Urogynecol J* 22: 401–405.

European Association of Urology (2015) *EAU guidelines: the best current evidence for clinical practice*. Available at: www.uroweb.org/guidelines (accessed 27 November 2015).

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

Gacci, M., Saleh, O., Giannessi, C., Detti, B., Livi, L., Monteleone Pasquetti, E. *et al.* (2015) Sodium hyaluronate and chondroitin sulfate replenishment therapy can improve nocturia in men with post-radiation cystitis: results of a prospective pilot study. *BMC Urol* 15: 65.

Giannessi, C., Villari, D., Saleh, O., Frizzi, J., Raugel, A., Li Marzi, V. *et al.* (2014) Nocturia related to post radiation bladder pain can be improved by hyaluronic acid chondroitin sulfate (Ialuril®). *Eur Urol* 13(Suppl.): e592.

Giberti, C., Gallo, F., Cortese, P. and Schenone, M. (2013) Combined intravesical sodium hyaluronate/chondroitin sulfate therapy for interstitial cystitis/bladder pain syndrome: a prospective study. *Ther Adv Urol* 5: 175–179.

Guay, D. (2008) Contemporary management of uncomplicated urinary tract infections. *Drugs* 68: 1169–1205.

Han, X., Wu, X., Li, B., Pan, F., Li, W., Liu, S., Zeng, F. *et al.* (2015) The effects of intravesical therapy with hyaluronic acid for painful bladder syndrome: preliminary Chinese experience and systematic review. *Taiwan J Obstet Gynecol* 54: 240–247.

Hanno, P., Baranowski, A. and Fall, M. (2005) Painful bladder syndrome (including interstitial cystitis). In: Abrams, P., Wein, A. and Cardozo, L. (eds), *Incontinence*, 3rd edn. Paris: Health Publications Limited, pp. 1456–1520.

Hanno, P., Burks, D., Clemens, J., Dmochowski, R., Erickson, D., Fitzgerald, M. *et al.* (2011) AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 185: 2162–2170.

Hurst, R., Roy, J., Min, K., Veltri, R., Marley, G., Patton, K. *et al.* (1996) A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. *Urology* 48: 817–821.

Iavazzo, C., Athanasiou, S., Pitsouni, E. and Falagas, M. (2007) Hyaluronic acid: an effective alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis? *Eur Urol* 51: 1534–1540.

Imperatore, V., Certa, M., Di Meo, S., Buonopane, R., Fusco, F., Imbimbo, C. *et al.* (2014) Intravesical instillation of sodium hyaluronate–chondroitin sulfate in patients with bacillus calmette-guérin-induced chemical cystitis unresponsive to conventional therapies: preliminary experience with 1 year follow-up. *Eur Urol Suppl* 13: e466.

Laupland, K., Ross, T., Pitout, J., Church, D. and Gregson, D. (2007) Community-onset urinary tract infections: a population-based assessment. *Infection* 35: 150–153.

Lazzeri, M. (2009) Editorial comment on: a refocus on the bladder as the originator of storage lower urinary tract symptoms: a systematic review of the latest literature. *Eur Urol* 56: 820.

Lazzeri, M. and Montorsi, F. (2011) The therapeutic challenge of 'chronic cystitis': search well, work together, and gain results. *Eur Urol* 60: 78–80.

Li Marzi, V., Del Popolo, G., Maurelli, V., Cocci, A., Perugia, C., Bove, P. *et al.* (2013) Intravescical administration of hyaluronic acid plus chondroitin sulphate to reduce local bacillus calmette guerin (BCG) toxicity: a randomized prospective pilot study. ICS 2013, 26–30 August 2013, Barcelona, Spain: abstract 554.

Lipovac, M., Kurz, C., Reithmayr, F., Verhoeven, H., Huber, J. and Imhof, M. (2007) Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. *Int J Gynaecol Obstet* 96: 192–195.

Maggi, C. and Meli, A. (1988) The sensory efferent function of capsaicin-sensitive neurons. *Gen Pharmac* 19: 1–43.

Morales, A., Emerson, L., Nickel, J. and Lundie, M. (1996) Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *J Urol* 156: 45–48.

Morelli, M., Mocciaro, R., Venturella, R., Albano, A., Sacchinelli, A. and Zullo, F. (2015) Hyaluronic acid-chondroitin sulfate: a potential factor to select pure stress urinary incontinence in patients with interstitial cystitis/painful bladder syndrome and mixed incontinence symptoms. *Minerva Ginecol* 67: 121–125.

Nickel, J., Egerdie, R., Steinhoff, G., Palmer, B. and Hanno, P. (2010) A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulphate *versus* vehicle control in patients with interstitial cystitis/painful bladder syndrome. *Urology* 76: 804–809.

Parsons, C. (2007) The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. *Urology* 69(Suppl. 4): 9–16.

Payne, H., Adamson, A., Bahl, A., Borwell, J., Dodds, D., Heath, C. *et al.* (2013) Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges. *BJU Int* 112: 885–897.

Porru, D., Cervigni, M., Nasta, L., Natale, F., Lo Voi, R., Tinelli, C. *et al.* (2008) Results of endovesical hyaluronic acid/chondroitin sulfate in the treatment of interstitial cystitis/painful bladder syndrome. *Rev Recent Clin Trials* 3: 126–129.

Porru, D., Leva, F., Parmigiani, A., Barletta, D., Choussos, D. and Gardella, B. (2012) Impact of intravesical hyaluronic acid and chondroitin sulphate on bladder pain syndrome/interstitial cystitis. *Int Urogynecol J* 23: 1193–1199.

Sculptoreanu, A., de Groat, W., Buffington, C. and Birder, L. (2005) Abnormal excitability in capsaicin-responsive DRG neurons from cats with feline interstitial cystitis. *Exp Neurol* 193: 437–443.

Serretta, V. (2014) Fibronectin (FN), epidermal growth factor-receptor (EGF-R) and heparin-binding epidermal growth factor-like (HB-EGF) urinary expressions and topical toxicity of adjuvant intravesical therapy for nonmuscle invasive bladder cancer (NMI-BC). *Eur Urol Suppl* 13: e409.

Shao, Y., Lu, G. and Shen, Z. (2012) Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. *BJU Int* 109: 691–694.

Sommariva, M., Lazzeri, M., Abrate, A., Guazzoni, G., Sandri, S. and Montorsi, F. (2014) Intravescial hyaluronic acid and chondroitin sulphate improve symptoms and quality of life in patients with late radiation tissue cystitis: an investigative pilot study. *Eur J Inflammation* 12: 177–185.

Sorlozano, A., Jimenez-Pacheco, A., de Dios Luna Del Castillo, J., Sampedro, A., Martinez-Brocal, A., Miranda-Casas, C. *et al.* (2014) Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: a 7-year surveillance study. *Am J Infect Control* 42: 1033–1038.

Steinhoff, G., Ittah, B. and Rowan, S. (2002) The efficacy of chondroitin sulphate 0.2% in treating interstitial cystitis. *Can J Urol* 9: 1454–1458.

Topazio, L., Miano, R., Maurelli, V., Gaziev, G., Gacci, M., Iacovelli, V. *et al.* (2014) Could hyaluronic acid (ha) reduce bacillus calmette-guerin (BCG) local side effects? Results of a pilot study. *BMC Urol* 14: 64.

Torella, M., Schettino, M., Salvatore, S., Serati, M., De Franciscis, P. and Colacurci, N. (2013) Intravesical therapy in recurrent cystitis: a multi-center experience. *J Infect Chemother* 19: 920–925.

Yoon, H., Byun, Y., Shim, B., Chung, W., Lee, D. and Parl, Y. (2013) Early experience of safety and efficacy of sodium hyaluronate-chondroitin sulfate solution in chronic painful conditions in the bladder. *Eur Urol Suppl* 12: e512.