Open Forum Infectious Diseases

NOVEL ID CASES

Hyaluronic Acid and Chondroitin Sulphate Treatment for Recurrent Severe Urinary Tract Infections due to Multidrug-Resistant Gram-Negative Bacilli in a Patient With Multiple Sclerosis: Case Report and Literature Review

Aurélien Dinh,[1] Clara Duran,[1] Kamel Hamami,[2] Muriel Afif,[2] Francine Bonnet,[3] Jean-Luc Donay,[4] Matthieu Lafaurie,[5] and Emmanuel Chartier-Kastler[6]

[1]Infectious Disease Department, Raymond-Poincaré University Hospital, Paris Saclay University, Assistance Publique–Hôpitaux de Paris, Garches, France, [2]Pharmacy, Raymond-Poincaré University Hospital, Paris Saclay University, Assistance Publique–Hôpitaux de Paris, Garches, France, [3]Anesthesiology Department, Saint-Louis University Hospital, University of Paris, Assistance Publique–Hôpitaux de Paris, Paris, France, [4]Microbiology Department, Saint-Louis University Hospital, University of Paris, Assistance Publique–Hôpitaux de Paris, Paris, France, [5]Infectious Disease Department, Saint-Louis University Hospital, University of Paris, Assistance Publique–Hôpitaux de Paris, Paris, France, and [6]Urology Department, Pitié-Salpétrière University Hospital, Paris Sorbonne University, Assistance Publique–Hôpitaux de Paris, Paris, France

Urinary tract infections (UTIs) are the most common bacterial infections in patients with neurogenic lower urinary tract dysfunction. Antibiotic options for prophylaxis or curative treatment in case of recurrent UTIs, especially due to multidrug-resistant organisms (MDRO), are scarce. We present the case of a 72-year-old man with neurogenic lower urinary tract dysfunction and history of frequent recurrent UTIs due to multiple MDROs who was successfully treated with hyaluronic acid (HA) and chondroitin sulfate (CS) bladder instillations. We also provide a literature review on the efficacy of HA-CS intravesical instillations for prevention of UTI among this population.

Keywords. antibiotics; hyaluronic acid; MDRO; neurogenic bladder; urinary tract infection.

Urinary tract infections (UTIs) are the most common bacterial infections in patients with neurogenic lower urinary tract dysfunction (NLUTD). Recurrent UTIs in this population lead to high antibiotic exposure and emergence of multidrug-resistant organisms (MDROs). Antibiotic options for prophylaxis or curative treatment in case of recurrent UTIs, especially due to MDROs, are scarce.

CASE REPORT

A 72-year-old man with a history of multiple sclerosis since the age of 19, presenting with severe neurocognitive disorders, motor weakness requiring a wheelchair, and NLUTD with reflex voiding and rectal incontinence, was treated with hyaluronic acid (HA) and chondroitin sulfate (CS) instillations for recurrent UTIs, including infections due to multidrug-resistant bacteria.

Throughout his past history of UTI, the patient's main signs of UTI were cloudy urine, tachycardia (heart rate >150 bpm), frequent hypotension requiring hospitalization in the emergency department or intensive care unit, and worsened neurological signs without other source of infection. The patient's UTI history is presented in Figure 1.

For each episode, symptoms prompted a urine culture, which yielded positive results, and antibiotic treatments were subsequently prescribed according to antibiotic susceptibility results. No antibiotics were prescribed without symptoms associated with positive urine culture.

The patient's first UTI occurred in 2012. From February 2014 to April 2021, the patient had 2–11 UTIs (febrile and not febrile) per year, sometimes due to MDROs. Due to voiding difficulties, a urethral endoprosthesis was inserted in 2014 and replaced in 2015, but definitively removed in 2017 due to migration in a bladder diverticulum leading to major hematuria. An urethrotomy was performed in May 2017. Cystoscopy with pyelograms revealed no fistula or nidus of infection.

In December 2018, the patient was prescribed a weekly oral cyclic antibiotic prophylaxis: alternate administration of amoxicillin and pivmecillinam once a week, according to our antibiotic prophylaxis protocol [1].

In June 2019, regular intermittent catheterization (4–5 times per day) was started and prophylactic measures were also enhanced: prevention of constipation through manual stool evacuation and specific diet, increased fluid intake, and oral intake

Received 27 January 2022; editorial decision 04 May 2022; accepted 10 May 2022; published online 12 May 2022

Correspondence: Aurélien Dinh, MD, PhD, Infectious Disease Department, Raymond-Poincaré University Hospital, AP-HP Paris Saclay University, 104 bd Raymond Poincaré, 92380 Garches, France (aurelien.dinh@aphp.fr).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac245

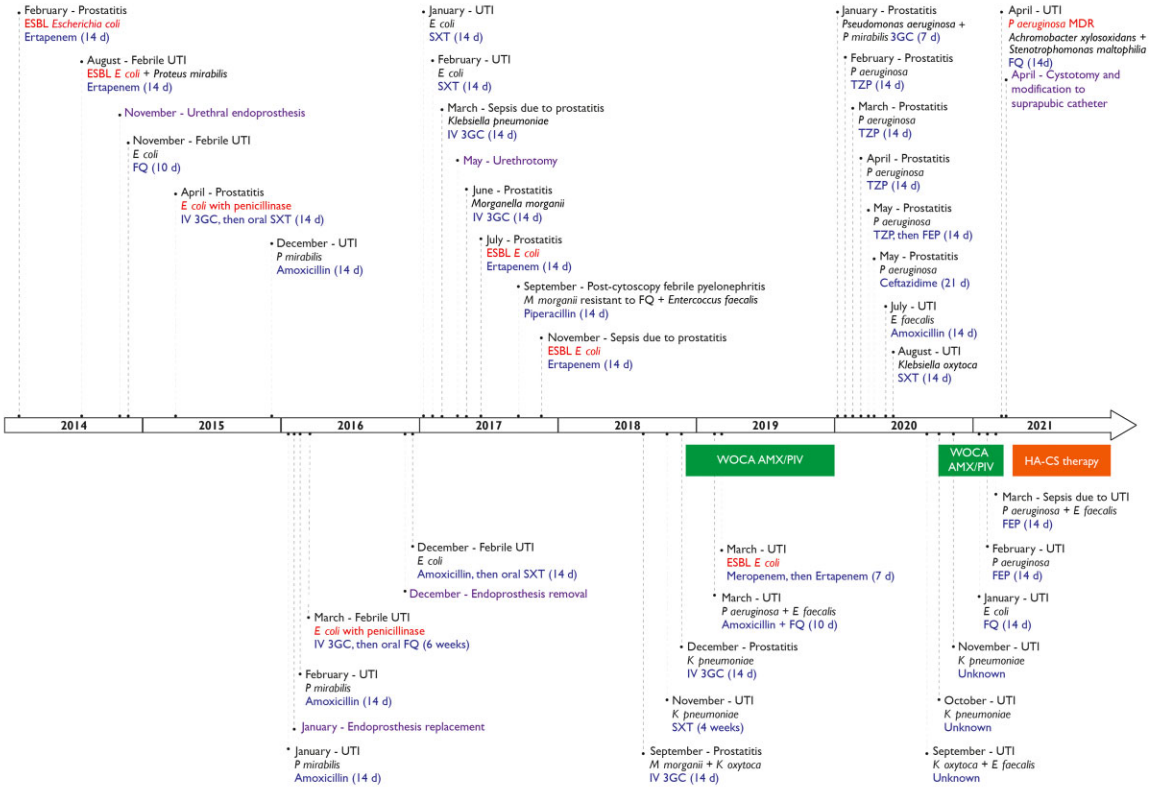

Figure 1. Patient's clinical history. Abbreviations: 3GC, third-generation cephalosporins; AMX, amoxicillin; d, days; ESBL, extended-spectrum β-lactamase; FEP, cefepime; FQ, fluoroquinolone; HA-CS, hyaluronic acid plus chondroitin sulfate; IV, intravenous; MDR, multidrug-resistant; PIV, pivmecillinam; SXT, sulfamethoxazole-trimethoprim; TZP, piperacillin-tazobactam; UTI, urinary tract infection; WOCA, weekly oral cyclic antibiotic prophylaxis.

of cranberry proanthiocyanidins. The patient had no UTI for 6 months, then UTIs recurred.

In April 2021, the patient had 2 new severe UTIs due to *Pseudomonas aeruginosa* and *Achromobacter xylosoxidans*, leading to hospitalization in the intensive care unit.

The voiding mode was then changed to suprapubic catheter to be changed regularly, and a new prevention strategy was initiated: glycosaminoglycan (GAG) therapy with HA-CS intravesical instillations through the suprapubic catheter. The protocol was a weekly instillation by a nurse during the first 2 weeks, then 1 instillation every 2 weeks. The patient received 50 mL of a sterile sodium HA 1.6% and CS 2.0% solution (IALURIL1, IBSA Farmaceutici, Lodi, Italy), carried out with the suprapubic catheter; the solution was retained in the bladder for at least 30 minutes. The nurse followed the protocol without any difficulties and reported no adverse event. No urological or medical specialist was required for the administration. Therefore, the HA-CS instillations could be performed by the patient on his own with a regular prescription, as the HA-CS solution is available in community pharmacies.

Since the first HA-CS instillation, the patient has had no UTI recurrence. Three urinalyses since first HA-CS administration indicated the presence of bacteriuria with *P aeruginosa*, without clinical symptoms of UTI.

DISCUSSION

We present the case of a patient with NLUTD, who was successfully treated for recurrent UTIs with HA-CS instillations. UTIs in patients with NLUTD are a major public health issue due to their high incidence and major consequences. Despite their frequency and potential severity, their physiopathology and management are poorly known. Regarding preventive measures, use of clean intermittent catheterization, intravesical botulinum toxin injection, and prevention using antibiotic cycling seem effective [1]. Bacterial interference is also promising, but further randomized controlled trials (RCTs) are needed [2]. Large ongoing cohorts and RCTs should provide evidence-based data on prophylaxis in these patients. To the best of our knowledge, there are no data on the use of HA-CS instillations among this population.

The interaction between bacteria and the epithelium of the bladder walls through the GAG layer lining is considered a

major factor in a patient's susceptibility to UTI [3, 4]. A damaged GAG layer could increase bacterial adherence and infection [5, 6]. Several methods were studied to reverse any GAG layer damage, using heparin [7], oral pentosan polysulphate [8], and hyaluronic acid, a major mucopolysaccharide widely found in epithelial tissues [9–11], which all conclude to the benefit of these treatments.

Furthermore, chondroitin sulphate, another component of the GAG layer, was also studied [12].

Therefore, we report herein the efficacy of using combined HA-CS intravesical instillations in the prevention of recurrent bacterial UTI in a patient with history of frequent UTIs due to MDROs. Moreover, antibiotic options for prophylaxis or curative treatment in case of UTI due to MDRO are scarce, especially with regard to oral regimen. Indeed, to treat infections due to *P aeruginosa*, no oral treatment is available, except for oral fosfomycin, anti–*Pseudomonas* fluoroquinolones, and possibly tetracyclines, but clinical data are lacking regarding the latter as well as the risk of resistance emergence with monotherapy on *P aeruginosa*.

The efficacy of HA-CS instillations has not been extensively studied. Overall, 10 original articles were found in a systematic literature review on PubMed, Cochrane, Scopus, and Embase databases, using the terms "hyaluronic acid and UTI," "hyaluronic acid and cystitis," and "hyaluronic acid and pyelonephritis," including 3 RCTs [10, 11, 13–20] (Table 1).

Table 1. Studies on Hyaluronic Acid and Chondroitin Sulfate Treatment for Recurrent Bacterial Urinary Tract Infections

Authors [Reference]	Patients	Study Design	Results
De Vita et al, 2018 [13]	Women with recurrent bacterial cystitis (N = 20)	RCT in 2 groups: intravesical instillation of HA-CS once weekly for 4 wk then once every 2 wk twice vs long-term antibiotic prophylaxis (SXT) once weekly for 6 wk; follow-up 36 mo	Cystitis rate in HA-CS group: –5.4 episodes/year ($P < .001$)
De Vita & Giordano, 2012 [14]	Women with recurrent bacterial cystitis (N = 28)	RCT in 2 groups: intravesical instillation of HA-CS once weekly for 4 wk then once every 2 wk twice vs long-term antibiotic prophylaxis (SXT) once weekly for 6 wk; follow-up 12 mo	Mean 12-mo rate of UTI after instillations vs antibiotic prophylaxis: 1 ± 1.2 vs 2.3 ± 1.4 ($P = .02$)
Damiano et al, 2011 [15]	Women with recurrent UTI (N = 57)	Double-blind RCT in 2 groups: intravesical instillation of HA-CS weekly for 4 wk and then monthly for 5 mo vs placebo; follow-up 12 mo	Mean rate of UTI after 12 mo: −86.6% ± 47.6 vs −9.6% ± 24.6 (mean difference, 77% [95% CI, 72.3–80.8]; $P = .0002$)
Ciani et al, 2016 [16]	Women with a history of recurrent UTI (N = 276)	Multicenter retrospective nested case-control study (2009–2013) in 2 groups: HA-CS once weekly for 4 wk, then once every 2 wk for 4 wk and once monthly thereafter (n = 181) vs standard of care prophylaxis (n = 95)	Confirmed UTI: 55.7% in the HA-CS group vs 62.1% in control group ($P = 0.313$)
Gugliotta et al, 2015 [17]	Women with a history of recurrent UTI (N = 174)	Multicenter retrospective cohort study in 2 groups: intravesical instillation of HA-CS once weekly for 4 wk then once monthly for 4 months, followed for a further 12 mo (n = 98) vs long-term antibiotic prophylaxis (SXT) once weekly for 6 wk (n = 76)	Proportion of patients free from UTIs at 12 mo: 36.7% vs 21.0% ($P = .03$)
Cicione et al, 2014 [18]	Women with a history of recurrent UTI (N = 157)	Multicenter retrospective cohort study in 2 groups: HA treatment (instillation once weekly for 4 wk, then once monthly for 5 mo, followed for up to 24 mo) vs retrospective review of patient records from before HA treatment	Mean number of UTIs per patient-year: 4.13 before HA-CS vs 0.44 after HA-CS ($P = .01$)
Torella et al, 2013 [19]	Women with recurrent bacterial cystitis (N = 69)	Prospective or retrospective study in 3 groups: intravesical instillation of HA-CS once a week for 4 wk, then once every 15 d for 2 mo, and finally once every 30 d for 2 mo (n = 22) vs oral fosfomycin (n = 23) 1 tablet every 10 d for 6 mo vs HA-CS and fosfomycin (n = 24)	Proportion of patients free from UTIs at 12 mo: 72.7% of patients in the HA-CS group, 30.4% in the fosfomycin group, 75% in the fosfomycin + HA-CS group
Costantini et al, 2013 [20]	Women with a history of recurrent UTI (N = 12)	Monocentric prospective cohort of patients receiving intravesical instillation of HA-CS (4 weekly instillations followed by 2 instillations every 2 wk and 2 instillations monthly)	8/12 patients with no UTI during 6-mo follow-up
Lipovac et al, 2007 [11]	Women with a history of recurrent UTI (N = 20)	2 groups: HA treatment (instillation once weekly for 4 wk, then once monthly for 5 mo, followed for a further 6 mo) vs retrospective review of patient records from before HA treatment	Mean rate of UTI per patient-year: 4.99 before HA vs 0.56 after HA ($P < .001$)
Constantinides et al, 2004 [10]	Women with a history of recurrent UTI (N = 40)	Pilot study in 2 groups: HA treatment (instillation once weekly for 4 wk, then once monthly for 4 mo, followed for a further 7 mo) vs retrospective review of patient records from before HA treatment	Mean rate of UTIs per patient-year: 4.3 before HA vs 0.3 after HA ($P < .001$)

Abbreviations: CA, chondroitin sulfate; CI, confidence interval; HA, hyaluronic acid; RCT, randomized controlled trial; SMT, sulfamethoxazole-trimethoprim; UTI, urinary tract infection.

Damiano et al conducted a randomized, double-blind, placebo-controlled trial comparing the efficacy of intravesical instillation of HA-CS in 57 women with recurrent UTIs over a 12-month follow-up period [15]. HA-CS intravesical instillations were found to significantly reduce the rate of UTIs without severe adverse effects, and improved symptoms and quality of life.

A second trial evaluated the effect of intravesical HA-CS vs antibiotic prophylaxis by sulfamethoxazole-trimethoprim in recurrent bacterial cystitis among 28 women over a 12-month follow-up period [14]. Intravesical HA-CS instillations significantly reduced cystitis recurrence and improved urinary symptoms and quality of life at 12-month follow-up.

In a prospective RCT comparing intravesical HA-CS vs long-term antibiotic prophylaxis (sulfamethoxazole-trimethoprim) among women with recurrent bacterial cystitis, cystitis recurrence and associated symptoms were significantly reduced in the HA-CS arm at 36 months [13].

Moreover, a nested case–control study in a large retrospective European cohort study was performed by Ciani et al [16]. Among 276 adult women treated for recurrent UTIs between 2009 and 2013, patients were treated with either intravesical administration of HA-CS or standard of care (eg, antibiotic or oral immunostimulant [OM-89] prophylaxis, probiotics, or cranberry). Results showed that HA-CS reduced the risk of UTI recurrence compared with the standard of care.

However, no RCT with sufficient power and large sample size has been performed on this promising strategy to assess efficacy. Therefore, more data are warranted in the general population, but also in specific populations with high risk of recurrent UTIs, as in patients with NLUTD.

Despite antimicrobial prophylaxis of recurrent UTIs representing an effective management option [18], nonantimicrobial prevention strategies are necessary to prevent bacterial resistance emergence. In addition, cost-effectiveness studies to compare the costs of a course of HA-CS intravesical instillations over a 12-month period to antibiotic prophylaxis are also needed.

Our case report showed the efficacy of bladder instillation of HA-CS in preventing UTI in a patient with NLUTD and history of recurrent UTIs due to multiple MDROs.

To best of our knowledge, no data on HA-CS intravesical instillations are available for prevention of UTI among this population, despite the major importance of preventing UTI in this specific population with high prevalence of MDRO infection [21]. Large multicenter studies are mandatory to confirm these encouraging results and to demonstrate the feasibility of this treatment option in patients with NLUTD and recurrent UTIs.

Notes

Patient consent. The patient's written consent was obtained before publication of this report. All patient-specific information has been anonymized as much as possible. No human subject experiments were conducted related to this case report; hence, local ethics committee approval was not indicated.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Dinh A, Hallouin-Bernard M-C, Davido B, et al. Weekly sequential antibioprophylaxis for recurrent urinary tract infections among patients with neurogenic bladder: a randomized controlled trial. Clin Infect Dis **2020**; 71:3128–35.
2. Darouiche RO, Hull RA. Bacterial interference for prevention of urinary tract infection. Clin Infect Dis **2012**; 55:1400–7.
3. Schilling JD, Mulvey MA, Hultgren SJ. Dynamic interactions between host and pathogen during acute urinary tract infections. Urology **2001**; 57:56–61.
4. Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. World J Urol **1999**; 17:415–20.
5. Nickel JC, Emerson L, Cornish J. The bladder mucus (glycosaminoglycan) layer in interstitial cystitis. J Urol **1993**; 149:716–8.
6. Lowell Parsons C. Epithelial coating techniques in the treatment of interstitial cystitis. Urology **1997**; 49:100–4.
7. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol **1994**; 73:504–7.
8. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. Urology **1997**; 49:93–9.
9. Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol **1996**; 156:45–8.
10. Constantinides C, Manousakas T, Nikolopoulos P, et al. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. BJU Int **2004**; 93:1262–6.
11. Lipovac M, Kurz C, Reithmayr F, et al. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. Int J Gynecol Obstet **2007**; 96:192–5.
12. Hurst RE, Roy JB, Min KW, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology **1996**; 48:817–21.
13. De Vita D, Madonia M, Coppola E, et al. Long-term efficacy of intravesical instillation of hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: 36 months' follow-up. Clin Exp Obstet Gynecol **2018**; 45:224–8.
14. De Vita D, Giordano S. Effectiveness of intravesical hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: a randomized study. Int Urogynecol J **2012**; 23:1707–13.
15. Damiano R, Quarto G, Bava I, et al. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur Urol **2011**; 59:645–51.
16. Ciani O, Arendsen E, Romancik M, et al. Intravesical administration of combined hyaluronic acid (HA) and chondroitin sulfate (CS) for the treatment of female recurrent urinary tract infections: a European multicentre nested case-control study. BMJ Open **2016**; 6:e009669.
17. Gugliotta G, Calagna G, Adile G, et al. Is intravesical instillation of hyaluronic acid and chondroitin sulfate useful in preventing recurrent bacterial cystitis? A multicenter case control analysis. Taiwan J Obstet Gynecol **2015**; 54:537–40.
18. Cicione A, Cantiello F, Ucciero G, et al. 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 **2014**; 8:E721–7.
19. Torella M, Schettino MT, De Franciscis P, et al. Intravesical therapy in recurrent cystitis: a multi-center experience. J Infect Chemother **2013**; 19:920–5.
20. Costantini E, Lazzeri M, Pistolesi D, et al. Morphological changes of bladder mucosa in patients who underwent instillation with combined sodium hyaluronic acid-chondroitin sulphate (Ialuril). Urol Int **2013**; 91:81–8.
21. Dinh A, Saliba M, Saadeh D, et al. Blood stream infections due to multidrug-resistant organisms among spinal cord-injured patients, epidemiology over 16 years and associated risks: a comparative study. Spinal Cord **2016**; 54:720–5.