International Urogynecology Journal (2022) 33:1125–1143
https://doi.org/10.1007/s00192-021-05042-z

REVIEW ARTICLE

Efficacy of antimicrobial intravesical treatment for uncomplicated recurrent urinary tract infections: a systematic review

Meghana Reddy[1] · **Philippe E. Zimmern**[1]

Received: 30 August 2021 / Accepted: 11 November 2021 / Published online: 4 January 2022

Abstract

Introduction and hypothesis Intravesical antimicrobials (IVA) provide a localized modality of treatment for recurrent urinary tract infections (rUTIs). Owing to the sporadic use of these treatments, we conducted a systematic review on the efficacy of IVA in the management of uncomplicated rUTIs.

Methods A systematic review was conducted for all English language articles from inception to April 2021 utilizing the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards with the following databases: PubMed, OVID Embase, Biomed Central, and Scopus. References were cross-examined for further articles. Risk of bias was assessed in the articles included using the Cochrane and Joanna Briggs Institute tools.

Results The initial search resulting in 476 titles led to 15 full-text articles. Of the 13 in the final review (2 RCTs), 3 used gentamicin and 10 used hyaluronic acid IVA. These included 764 participants, mostly women, with a mean age range of 27–80 (median: 53.1). There was a reduction in UTI frequency in 12 out of 13 studies, with 10 studies showing a statistically significant decrease. Dosages of 80 mg of gentamicin per instillation and both 40 mg and 800 mg of hyaluronic acid per instillation were found to be effective in reducing the frequency of UTIs in most studies. Eleven participants reported gentamicin-resistant infections after IVA treatment. Despite high levels of bias in selected categories, the 13 studies were designated to be of high quality for inclusion.

Conclusions The IVAs gentamicin and hyaluronic acid with chondroitin sulphate demonstrated efficacy in the management of uncomplicated rUTIs, mostly in women.

Keywords Intravesical antimicrobials · Recurrent · UTI · Urinary infection · Treatment

Abbreviations

IVA	Intravesical antimicrobials
PUF	Pelvic pain and urgency/frequency
rUTIs	Recurrent urinary tract infections
UTIs	Urinary tract infections

Introduction

Urinary tract infections (UTIs) are a common type of bacterial infections in women. It is estimated that up to 50% of women develop at least one UTI in their lifetimes, with as many as 25% having at least one recurrence [1]. Recurrent UTIs (rUTIs) are typically defined as symptomatic episodes occurring at least twice in a 6-month period or three times in a 1-year period [2]. Recurrent UTIs have been postulated to be caused by two main mechanisms, either repeated ascending infections or chronic infections in the bladder [3]. Recent research advances have also identified bacteria unique to the urinary microbiome in rUTI pathobiology. Therefore, further research is needed to understand these interactions [4]. A review from Glover et al. [3] cites animal models to demonstrate the persistence of infection through quiescent intracellular bacterial reservoirs that are protected by biofilms. Additionally, recent data from De Nisco et al. indicated the presence of resident bacteria in the bladder wall biopsies of post-menopausal women with rUTIs, confirming the presence of deep-seated niches of infection in some patients [5]. Taken together, these data suggest that the etiology of infection in the bladder might be important for the management of uncomplicated rUTIs.

✉ Philippe E. Zimmern
Philippe.Zimmern@UTSouthwestern.edu

Meghana Reddy
Meghana.Reddy@UTSouthwestern.edu

[1] Department of Urology, U.T. Southwestern Medical Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9110, USA

Management options for rUTIs can be divided into non-antimicrobial and anti-microbial therapies. Estrogen supplementation, increased fluid intake, probiotics, cranberry, D-mannose, and methenamine hippurate have shown limited success in preventing UTIs [6]. Prophylactic antibiotic therapy has also been recommended, but this approach has raised concerns owing to cost, allergy, resistance, and side effects. Therefore, direct administration of antimicrobial agents in the bladder has been considered. Although the intravesical antimicrobial (IVA) approach has been part of clinical practice since the 1960s, IVAs have typically been reserved as end-of-line management strategies, and thus infrequently used.

With the rise in antimicrobial resistance, there is a need to understand all effective treatment modalities for rUTIs [7]. The aim of this systematic review is to recapitulate all available data on the efficacy of IVAs in the management of uncomplicated RUTIs.

Materials and methods

This systematic review was performed in accordance with Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [8]. A comprehensive review was performed on articles published from inception to April 2021 in the following databases: PubMed MEDLINE, OVID Embase, Biomed Central, and Scopus. Additionally, the references of the articles were searched by hand individually by the reviewers to identify any additional articles that may have been otherwise missed by search engines.

The following are the criteria for including studies in this review.

Inclusion criteria:

- All full text, English-language prospective cohort, retrospective cohort, and randomized control trial studies of female patients over the age of 18
- Studies explicitly focused on the intravesical administration of antimicrobial treatment for uncomplicated recurrent UTIs
- "Antimicrobial" treatment defined as both traditional antibiotic and non-antibiotic therapies targeting bacteria

Exclusion criteria:

- Individual case reports, review articles, nonhuman studies, abstracts-only texts
- Studies with male-only or pediatric-only populations; note that studies including both men and women were not excluded to optimize the limited dataset
- Studies reporting IVA treatments for complicated rUTIs with underlying secondary pathology, including but not limited to neurogenic bladder, catheterization, or spinal cord injury
- Studies reporting non-antimicrobial intravesical treatments, including Botox injections

The search was conducted using the following key words: "Urinary tract infection," "lower urinary tract dysfunction," "recurrent urinary tract infection," "intravesical drug administration," "antibiotic treatment," and "anti-microbial treatment." Alternative spellings, names, and abbreviations of these keywords were searched. Keywords appeared in the title, abstract, or both. The following medical subject headings were used: "urinary tract infection" AND "intravesical administration" AND "anti-infective agents."

A total of 476 titles were initially collected. For the first round of extractions, the titles of the articles were reviewed and were excluded if they explicitly did not meet study criteria or were duplicates. Sixty-eight abstracts were further reviewed, from which 15 articles were selected for full-text review. Two independent trained and experienced reviewers (MR and PZ) evaluated all selected articles with a similar methodology.

Following PRISMA guidelines, risk of bias was assessed for each full-text study included. The Cochrane Risk of Bias Tool for Randomized Control Trials was used for critical appraisal. The tool utilizes 7 main domains to assess bias on a scale of judgment (high, low, or unclear). The Joanna Briggs Institute critical appraisal checklist for non-RCTs was used for the remaining studies in this review [9].

Results

Thirteen studies were included in the final review (Fig. 1, flowchart). This included 2 RCTs, 4 prospective studies, 6 retrospective studies, and 1 study that used both retrospective and prospective analysis [10–23]. The countries of origin included Italy ($n=6$), United Kingdom ($n=3$), United States ($n=1$), Greece ($n=1$), Austria ($n=1$), and the Netherlands ($n=1$).

Definition and diagnosis of UTI

The definitions of recurrent UTI are included for each study in Table 1. Eleven out of 13 studies defined recurrent UTI with a culture confirmed method, with the lowest threshold at 10^3 colony-forming units/ml. A few studies did not specify culture confirmation as a diagnostic tool and based their UTI diagnosis on symptomatology alone.

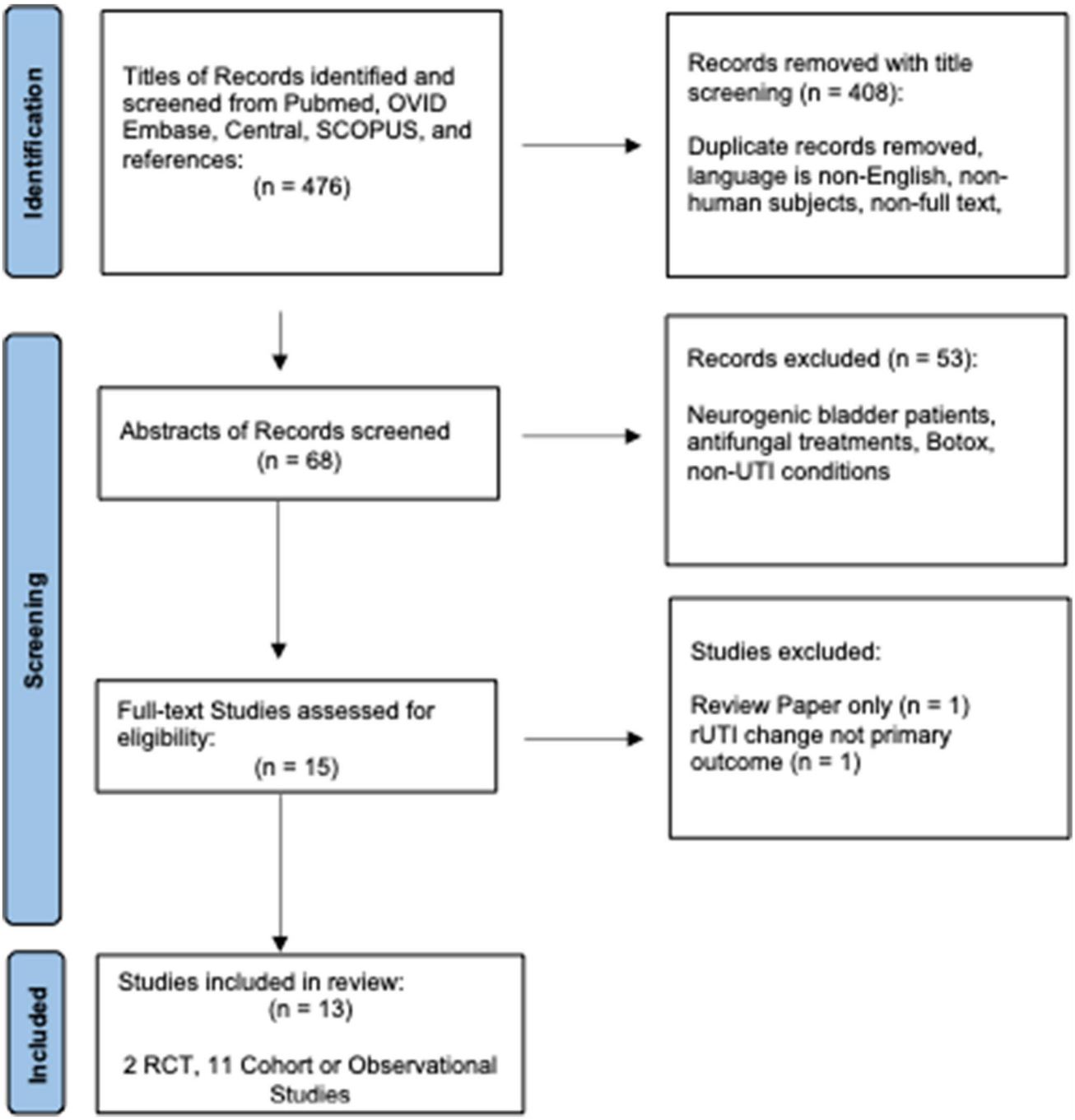

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

Baseline population characteristics

With these studies combined, a total of 761 participants received IVA treatment. Specifically, 3 studies administered gentamicin IVA and the remaining 10 studies administered hyaluronic acid (HA) and chondroitin sulfate (CS). The mean age range of the participants in the studies included was 27–80 (median 53.1). Eleven studies had female participants only and the remaining 2 studies had a male to female ratio of 1:4 (74–77%). Most IVA participants had uncomplicated recurrent UTIs and failed oral antibiotic therapies (Table 1). The number of failed oral antibiotic treatments needed to qualify for IVA differed across studies or were not specified in most of the studies. Only Abrams et al. specified that women in whom double oral antibiotic treatment failed qualified for IVA [21].

Table 1 Baseline characteristics of all the studies included

Type of study	Publication date	Journal	Author/references	Country	Intravesical antimicrobial	Author's definition of included patients with rUTI	Primary objective	Number of patients (treatment completed)	Number of female (%)	Mean age (years)
RCT	2011	European Urology	Damiano et al. [10]	Italy	HA + CS	A UTI episode was defined in the form of bacteriuria as $>10^{-3}$CFU/ml of midstream urine with clinical symptoms	We report the results of a prospective, randomized, double-blind, placebo-controlled trial aiming to investigate the efficacy and tolerability of intravesical administration of combined HA and CS in reducing the rate of UTI and improving the quality of life in female patients with a history of recurrent UTI.	54	54 (100)	34.8
RCT	2012	The International Urological Association	De Vita and Giordano [11]	Italy	HA + CS	At least three episodes of uncomplicated cystitis with clinical symptoms and/or a positive culture for each episode, defined as the isolation of more than 103 CFU of a uropathogen per milliliter of urine	The aim of this study was to evaluate with a prospective randomized study the beneficial action of intravesical therapy with HA-CS compared with long-term antibiotic prophylaxis in reducing the occurrence for the treatment of recurrent bacterial cystitis.	26	26 (100)	59

Table 1 (continued)

Type of study	Publication date	Journal	Author/references	Country	Intravesical antimicrobial	Author's definition of included patients with rUTI	Primary objective	Number of patients (treatment completed)	Number of female (%)	Mean age (years)
Prospective cohort study	2004	BJU International	Constantinides et al. [12]	Greece	HA + CS	Only patients with a documented positive culture for each infection were included, a positive culture being defined as the isolation of a uropathogen at > 1,063 CFU/ml	In the present pilot study we assessed the effect of HA on the rate of recurrence of UTIs in patients with a history of recurrent UTI.	40	40 (100)	35
Prospective cohort study	2007	International Journal of Gynaecology and Obstetrics	Lipovac et al. [13]	Austria	HA + CS	At least three episodes of uncomplicated cystitis with clinical symptoms and/or a positive culture for each episode, defined as the isolation of more than 103 CFUs of a uropathogen per milliliter of urine	To evaluate the efficacy of vesical instillation of hyaluronic acid against recurrent urinary tract infections.	20	20 (100)	27.7
Prospective cohort study	2012	Current Urology	Raymond et al. [14]	United Kingdom	HA + CS	Recurrent UTI is defined as two uncomplicated UTIs in 6 months or, more traditionally, as three positive cultures within the preceding 12 months	We present our initial results in the use of 40 mg intravesical sodium hyaluronate in patients with PBS/IC and recurrent UTIs who have completed treatment.	13	10 (77)	36.4

Table 1 (continued)

Type of study	Publication date	Journal	Author/references	Country	Intravesical antimicrobial	Author's definition of included patients with rUTI	Primary objective	Number of patients (treatment completed)	Number of female (%)	Mean age (years)
Prospective non-randomized trial	2019	The Journal of Urology	Stalenhoef et al. [15]	The Netherlands	Gentamicin	Preceding UTIs were defined by self-report but 1 or more UTI episodes had to be documented by urine culture with the isolation of 103 CFU/ml or greater of an identified MDR pathogen	This prospective study was aimed at assessing the effectiveness, safety, and feasibility of intravesical gentamicin in patients with refractory rUTI.	53	53 (100)	27.7
Prospective or retrospective analysis	2013	Journal of Infection and Chemotherapy	Torella et al. [17]	Italy	HA + CS	At least two episodes of infection without any complication in the previous 6 months or at least three episodes in the previous 12 months. The infection was confirmed by positive urine cultures, which in most cases were positive for *Escherichia coli*	The aim of our study was to assess whether intro vesical therapy with hyaluronic add and chondroitin sulfate is more effective than antibiotic therapy in reducing episodes and symptoms of recurrent urinary tract infections.	69	69 (100%)	59

Table 1 (continued)

Type of study	Publication date	Journal	Author/references	Country	Intravesical antimicrobial	Author's definition of included patients with rUTI	Primary objective	Number of patients (treatment completed)	Number of female (%)	Mean age (years)
Retrospective cohort study	2014	Canadian Urological Association Journal	Cicione et al. [18]	Italy	HA + CS	At least three episodes of uncomplicated UT1s with the isolation of >103 CI U/ml of an identified pathogen with clinical symptoms in the last 12 months	This study was initiated as a collaborative effort to provide a review of outcomes from centers pioneering the intravesical instillation of HA 1.6% plus CS 2% for prophylaxis of recurrent urinary tract infections in female patients.	157	157 (100)	53.1
Retrospective nested case–control	2015	The BJM	Ciani et al. [19]	Italy	HA + CS	At least three episodes of uncomplicated UTIs accompanied by clinical symptoms and documented by urine culture with the isolation of >103 CFU/ml of an identified pathogen in the past 12 months	The primary outcome for this study was the occurrence of objective UTI recurrence, defined as the occurrence of at least one bacteriologically confirmed UTI within 12 months after treatment initiation for rUTIs.	181	181 (100)	55

Table 1 (continued)

Type of study	Publication date	Journal	Author/references	Country	Intravesical antimicrobial	Author's definition of included patients with rUTI	Primary objective	Number of patients (treatment completed)	Number of female (%)	Mean age (years)
Retrospective cohort study	2015	Taiwanese Journal of Obstetrics & Gynecology	Gugliotta et al. [20]	Italy	HA + CS	At least three episodes of uncomplicated cystitis in the past year, with clinical symptoms and/or positive culture for each episode (a positive culture being defined as the isolation of >103 CFU of a uropathogen per milliliter of urine)	The present study compared HA & CS intravesical instillation with long-term antibiotic prophylaxis in terms of efficacy and tolerability in women with recurrent UTI.	96	96 (100)	36.4
Retrospective cohort study	2017	Neurourology and Urodynamics	Abrams et al. [21]	United Kingdom	HA + CS	Six or more culture-confirmed UTIs over a 12-month period or at least one hospital admission as a result of UTI	The objective of this study was to assess the efficacy, safety, and tolerability of intravesical gentamicin for treating patients with LUTE and multiple or serious refractory UTIs and to review previous literature on the use of intravesical aminoglycosides.	22	20 (74)	55

Table 1 (continued)

Type of study	Publication date	Journal	Author/references	Country	Intravesical antimicrobial	Author's definition of included patients with rUTI	Primary objective	Number of patients (treatment completed)	Number of female (%)	Mean age (years)
Retrospective observational outcome	2020	International Urology and Nephrology	Batura et al. [22]	United Kingdom	HA + CS	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last 6 months	Our objective was to observe changes in UTI severity and quality of life after treatment with interstitial SH.	18	18 (100)	75
Retrospective case series	2020	Female Pelvic Medicine Reconstructive & Surgery	Chernyak and Salamon [23]	United States	Gentamicin	Two or more infections in a 6-month period as determined by urine culture, with a colony count of 1.105 via the clean-catch route or ≥103 via the catheterized route	We have been performing intravesical instillations in our institution, and the aim of this article is to share our clinical experience of antibiotic bladder instillations for the treatment of recurrent UTIs in post-menopausal women.	12	12 (100)	80.3

CS chondroitin sulfate, *HA* hyaluronic acid, *IC* interstitial cystitis, *LUTE* lower urinary tract exercises, *MDR* multidrug resistance, *PBS* painful bladder syndrome, *rUTI* recurrent urinary tract infection, *SH* sodium hyaluronate, *UTI* urinary tract infection

Outcomes

Details of the IVA interventions and outcomes are presented in Table 2. All three studies including IVA gentamicin mentioned doses of 80 mg per instillation. There was variability in the amount of solution in which the 80 mg gentamicin was dissolved, ranging from 20 to 60 ml. The frequency of the instillations during the treatment duration varied from 6 to 73. For example, the Chernyak and Salamon study prescribed instillations to participants twice a week for 3 weeks, whereas the Stalenhoef et al. study prescribed instillations to participants once a day for 2 weeks, following which participants received instillations every other day for 10 weeks and then twice weekly for 12 weeks. There was a long follow-up time after these instillations in each of these studies of at least 6 months. Within the 10 studies that included IVA of HA and CS, 6 studies dosed each instillation at 800 mg (1.6%) of HA and 1 g (2%) of CS in 50 ml solution. The remaining 4 studies dosed the HA at 40 mg in 50 ml solution. Additionally, the follow-up time ranged in these studies from 6 weeks to 20 months. The number of HA + CS instillations ranged from 6 to 10 across the studies.

RCT outcome descriptions

In the RCT by De Vita and Giordano, the primary outcome was the number of UTI episodes, which reported a post-hoc statistical power of 0.023. The treatment group, which received a commercially available IVA of HA + CS, was compared with the control group, which received only oral antibiotic prophylaxis. In the RCT by Damiano et al., the primary outcome was the mean rate of UTI episodes per patient per year. In the study a power of 30 subjects per group was calculated to be necessary to detect an induced difference in a 70% decrease of the UTI rates between groups. The treatment group, which received a commercially available IVA of HA + CS was compared with a control group that received placebo instillations.

Effect of IVA

Most participants who underwent IVA instillations experienced positive outcomes. All three gentamicin studies (87 participants) reported decreases in UTI recurrence after completion of the IVA instillations compared with before IVA. In the study by Stalenhoef et al., the mean number of UTIs decreased from 4.8 to 1.2 ($p < 0.001$). In the study by Chernyak and Salamon, the mean UTI frequency was reduced from 2.5 to 1.5 UTIs ($p = 0.025$). Additionally, 9 out of 10 studies with IVA of HA and CS (674 participants) reported a decrease in UTI recurrence. Of these studies, 8 showed a statistically significant decrease in UTI recurrence. Of note, the study by Ciani et al. reported a greater number of UTI recurrences in the HA + CS group compared with the standard care group; however, the authors stated that when adjusted for the incidence risk ratio, there were non-significant differences in the treatment and control groups. There was an overall mean decrease of 2.3 UTIs/year in the gentamicin studies and 4.03 UTIs/year across the HA + CS studies.

The discontinuation rates ranged from 0% to 22% in the gentamicin studies. A total of 5 participants (7.42%) dropped out of the treatment course across all HA + CS studies. The most frequently cited reason was loss to follow-up. Adverse events were minimal across all studies. Of the gentamicin studies, the study by Stalenhoef et al. reported IVA side effects of abdominal discomfort (5%), hearing loss (3%), and vaginal discomfort (20%). In the HA and CS studies, only minor side effects were cited. Resistance to treatment rates were reported in 2 gentamicin studies. The studies by Abrams et al. and Stalenhoef et al. reported 11 patients with gentamicin-resistant infections after instillation treatment. None of the HA + CS studies reported resistance rates after treatment.

Risk of bias

Of the 13 studies included in this review, 2 studies were identified as RCTs and the Cochrane Risk of Bias Tool for Randomized Control Trials was used for these 2 studies. The Joanna Briggs Institute critical appraisal checklist for non-RCTs was used for the remaining 11 studies in this review.

A summary of the risk of bias assessment for the studies is provided in Tables 3 and 4. The majority of the non-RCT studies studied outcomes in the same group of participants before and after IVA treatment, leading to minimal differences in exposures between the two groups for comparison. We found that most of the studies did not explicitly identify strategies in dealing with confounding variables. Despite high levels of bias in select categories, we found the quality of the 13 studies to be high enough for inclusion.

Discussion

Echoing recent American Urological Association (AUA) guidelines on rUTIs, this review focused on uncomplicated rUTI treatments and explored the efficacy of intravesical antimicrobial therapy for uncomplicated recurrent UTIs in a predominantly female population [24]. The search yielded two frequently used antimicrobials: gentamycin and hyaluronic acid with chondroitin sulfate therapy. Both therapies yielded a successful decrease in recurrent UTI

Table 2 Intervention characteristics and primary outcomes of the studies included

Study	Intravesical antimicrobial	Administration	Dose	Frequency of treatment	Mean number of installations	Follow-up range	Successful outcome (decrease in UTI recurrence)	Discontinuation	Reasons	Treatment resistance	Side effects
Abrams et al. [21]	Gentamicin	Self	80 mg dissolved in 50 ml of sterile water or 0.9% sodium chloride	Varied from nightly regime, twice weekly, one every other day, one every 5 days for different numbers of months	NR	12 months	22/27(81.96%)	6/27(22%)	Bladder stone found for treatment, nonfunctioning kidney removed, cystectomy, high serum potassium, persistent infections, death, new onset diarrhea	5 patients had gentamicin-resistant infections	No major SE reported
Chernyak and Salamon [23]	Gentamicin	Outpatient nurse practitioner	80 mg dissolved in 60 ml normal saline	Twice weekly for 3 weeks	6	6 months	Median of 2.5 UTIs/6 months before to 1.5 UTIs ($p = 0.025$)	0	N/A	Median total antibiotics pathogens resistant was 8.5 before treatment to 0 after treatment	No major SE Reported
Stalenhoef et al. [15]	Gentamicin	Self or home nurse	80 mg dissolved in 20 ml 0.9% sodium chloride	Daily for 2 weeks, every other day for 10 weeks and twice weekly for 12 weeks (24 weeks)	73	6 months	Mean of 4.8 to 1.2 ($p < 0.001$)	7/60 (11.8%)	Clinical failure, withdrawal due to surgery, chemotherapy planned pregnancy	6 patients had gentamicin-resistant infections[b]	3 (5%) abdominal discomfort, 2 hearing loss (3%), 10 (20%) vaginal discomfort

Table 2 (continued)

Study	Intravesical antimicrobial	Administration	Dose	Frequency of treatment	Mean number of installations	Follow-up range	Successful outcome (decrease in UTI recurrence)	Discontinuation	Reasons	Treatment resistance	Side effects
Batura et al. [22]	HA + CS	Urology nurse practitioner in outpatient setting	40 mg dissolved in 50 ml for first 6 weeks, then switched to 120 mg in 50 ml for induction or with self-perceived relapses	Weekly for 6 weeks. If symptoms persisted or recurred, patients received 120 mg/50 ml on-demand	8	6+ weeks	Median of 10 per year to 2 per year after treatment	0	N/A	NR	No adverse events occurred during or after treatment. Most patients reported a burning discomfort during and immediately after instillations
Ciani et al. [19]	HA + CS	NR	800 mg (1.6%) of HA and 1 g of CS (2%) in 50 mL	One instillation per week for the first month, followed by one instillation every 2 weeks for the second month and one instillation per month afterward until stable remission of symptoms	7+	12 months	121 UTI recurrences with HA + CS versus 51 UTI recurrences with standard care[a]	0	N/A	NR	NR
Cicione et al. [18]	HA + CS	NR	800 mg (1.6%) of HA and 1 g of CS (2%) in 50 mL	One instillation per week for 4 weeks and then monthly for 5 months (maintenance phase)	9	12 months	4.13 recurrences/person/year to 0.44 recurrences/person/year (p =0.01)	0	N/A	NR	NR

Table 2 (continued)

Study	Intravesical antimicrobial	Administration	Dose	Frequency of treatment	Mean number of installations	Follow-up range	Successful outcome (decrease in UTI recurrence)	Discontinuation	Reasons	Treatment resistance	Side effects
Constantinides et al. [12]	HA + CS	Outpatient setting	40 mng of HA in 50 ml	One instillation per week for 4 weeks and then one instillation monthly for 4 months	8	6 months	Mean decrease of 4.8 infections; mean decrease of 4 UTIs per patient/year ($p < 0.05$)	3	Lost to follow-up	NR	No serious adverse events were reported. Nine women (23%) reported mild bladder irritation but the symptoms did not last for >6 h after the instillation and 3 women required anti-inflammatory medication to relieve the symptoms
Damiano et al. [10]	HA + CS	Nurse practitioner	800 mg (1.6%) of HA and 1 g of CS (2%) in 50 mL	One instillation per week for 4 weeks, then monthly for 5 months	9	12 months	Mean number of UTIs of 4.19 (placebo group) versus 0.67 (HA + CS group) at 12 months ($p < 0.001$)	2	Lost to follow-up	NR	Three patients on HA + CS(11.1%) reported moderate storage urinary symptoms, in the absence of infection, but only one required anti-inflammatory medication for symptom relief
De Vita and Giordano [11]	HA + CS	Outpatient setting	800 mg (1.6%) of HA and 1g of CS (2%) in 50 ml	One instillation weekly for 4 weeks, following one instillation every 2 weeks twice	5	12 months	2.3 UTIs to 1 at 12-month follow-up ($p = 0.02$)	0	NA	NR	NR

Table 2 (continued)

Study	Intravesical antimicrobial	Administration	Dose	Frequency of treatment	Mean number of installations	Follow-up range	Successful outcome (decrease in UTI recurrence)	Discontinuation	Reasons	Treatment resistance	Side effects
Gugliotta et al. [20]	HA + CS	NR	800 mg (1.6%) of HA and 1 g of CS (2%) in 50 ml	One instillation weekly for 4 weeks, following one instillation monthly for 4 months	8	12 months	Total number of UTIs is 109 (placebo) and 69 (HA + CS) at 12 months ($p = 0.03$)	0	N/A	NR	NR
Lipovac et al. [13]	HA + CS	NR	40 mg in 50 ml of PBS	One instillation weekly for 4 weeks, following one instillation monthly for 5 months	9	12 months	3.4 to 0.5 UTIs per patient ($p < 0.001$); infection rate per patient-year 4.99 to 0.56 ($p < 0.001$)	0	N/A	NR	There were 18 women (90%) who reported mild to moderate pain during the instillation and 6 (30%) who reported cramping or burning up to 2 days after an instillation. Three women required anti-inflammatory medication to relieve the symptoms
Torella et al. [17]	HA + CS	NR	800 mg (1.6%) of HA and 1 g of CS (2%) in 50 ml	One instillation weekly for 4 weeks, following one instillation every 15 days for 2 months, following 1 instillation every 30 days for 2 months	10	20 months (mean)	16 patients (standard care) experienced recurrence vs 6 patients (HA + CS group) at 6-month follow-up ($p = 0.0029$)	0	N/A	NR	NR

Table 2 (continued)

Study	Intravesical antimicrobial	Administration	Dose	Frequency of treatment	Mean number of installations	Follow-up range	Successful outcome (decrease in UTI recurrence)	Discontinuation	Reasons	Treatment resistance	Side effects
Raymond et al. [14]	HA + CS	NR	40 mg of HA in 50 ml	One instillation per week for 4 weeks, following one instillation per month	9	21 months (mean)	Frequency of UTIs not reported—symptomology change reported. Significant improvement in bladder pain ($p = 0.0005$), day- time frequency ($p = 0.0354$) and QoL ($p = 0.0207$) was noted	7	Stopped prematurely owing to clinical failure	NR	NR

CS chondroitin sulfate, *HA* hyaluronic acid, *N/A* not applicable, *NR* not reported, *PBS* phosphate-buffered saline, *SE* side effect, *UTI* urinary tract infection

[a]Adjusted incidental relative risk rates show nonsignificant differences between HA + CS and standard care

[b]A total of 9 patients had gentamicin UTIs, but 3 of these patients were treated with a nongentamicin instillation at baseline

Table 3 Risk of bias assessment of the randomized control trials included in this review. The Cochrane risk of bias tool for randomized control trials was used

Reference	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding of participants	Blinding outcome assessment	Incomplete outcome data
Damiano et al. [10]	Low	Low	Low	Unclear	Low	Low	Low
De Vita and Giordano [11]	Low	Low	Unclear	Unclear	High	High	Low

rates, with an overall mean decrease of 2.3 UTIs/year in the gentamicin studies and 4.03 UTIs/year across the HA + CS studies.

Intravesical drug administration provides a localized target for delivery. The urothelium lining provides a strong barrier that allows administered drugs to achieve a localized luminal effect on the planktonic bacteria while minimizing reabsorption, thus leading to fewer systemic adverse effects [25]. Even at considerably high dosages, absorption of IVA has been minimal when tested with blood serum levels. Intravesical gentamicin has been able to combat multi-resistant *E. coli* in the bladder [26]. The efficacy of HA and CS agents is related to their ability to replenish the glycosaminoglycan (GAG) layer at the bladder surface [25]. Evidence surrounding this GAG layer theory has been supported by various animal models, such as in porcine or rat cells [27, 28].

This review underscores the high level of efficacy of IVAs in women with uncomplicated rUTIs failing repeated oral antibiotic courses. Gentamicin provided a significant decrease in UTIs at least up to 6 months after IVA treatment. Because the frequency of instillations differed across studies, ranging from 6 to 73, it was not possible to determine the optimal number of instillations to reach a favorable outcome. Of note, all three studies used the same dosing of 80 mg of gentamicin per instillation, demonstrating the efficacy of the dosage. Although IVAs are generally seen as less likely to cause antimicrobial resistance than oral antibiotics owing to its localized effect, two of the gentamicin studies included reported gentamicin-resistant infections in patients after at least 6 months of treatment exposure. Evidence is limited in the resistance to gentamicin after several months of bladder instillation exposure.

The European market offers two different formulations of HA and CS IVA, either 0.08% HA (40 mg) or 1.6% HA (800 mg) [25]. Most of the studies included utilized the 800-mg dosage, but both dosages were found to be efficacious for UTI reduction. A 2017 review highlighted HA and CS therapy as a novel strategy to reduce the risk of potential drug resistance that could be found when using other IVAs, such as with gentamicin in limited cases [29]. Although there is preliminarily research touting the efficacy of HA IVA, this therapy is not available in the United States for therapeutic use owing to the lack of FDA approval [30].

Cost of treatment is an important aspect of rUTI management. According to the Medicare fee service program, the national average cost of one intravesical instillation of gentamicin is $82.90 [31]. The cost of a commercially available HA + CS instillation, named iAluRil, is £105.60 ($146.81) in the United Kingdom [32]. Comparing cost efficacy across treatment regimens is difficult owing to unstandardized protocols; however, all studies included in this review used at least six instillations per patient to find significant utility in IVA. Using a minimum of 6 instillations per course would bring the total cost of gentamicin IVA to $497.4 and for HA + CS IVA to $880.86 per treatment course. Even though IVA treatments tend to be costlier than oral antibiotics and other conservative therapies, they are less expensive than IV antibiotics, which would be similarly used for more recurrent infections [33].

Limitations and areas of future research

Our review was limited by the nature of the studies (observational or cohort), with only two RCTs. Owing to the high level of heterogeneity across study designs and types, it was not possible to compare the outcomes across these studies through a meta-analysis. Additionally, two studies had a limited number of male participants in their cohort that were not separately analyzed [14, 21]. These two studies were not excluded from this review but explains why our conclusions stipulate that the reported data were "mostly for women."

There is a greater need for RCTs on IVA therapy in female participants with rUTIs. Particularly, greater efforts in exploring other antimicrobial therapies could be beneficial in expanding the field of intravesical treatments. Other IVA therapies have been reported but are limited to case reports or are not large-scale studies [34]. For example, in 2004 Wood et al. described a case of tobramycin IVA used to treat UTI in a 69-year-old woman. This patient had a protracted hospital course during which she developed *Enterobacter cloacae*, which was only susceptible to cefotetan and tobramycin [35]. Additionally, the study by Dutta and Lane found promising results in which 39 women were treated weekly with heparin IVA at a dose of 10,000 units mixed with 250 mg solumedrol in each instillation over the course of 6 weeks [36]. In the study by Stalenhoef et al., 3 patients were treated with a different

Table 4 Risk of bias assessment of the nonrandomized controlled trials included in this review. Joanna Briggs Institute critical appraisal checklist for non-RCTs was used

Reference	Two groups similar	Exposures similar	Exposure measured in a valid way	Confounding factors identified	Strategies to deal with confounding variables	Groups free outcome at start of study	Outcome measure in a valid way	Valid follow-up time	Follow-up complete	Strategies to address incomplete follow-up	Appropriate statistics	Overall appraisal
Abrams et al. [21]	Yes	N/A[b]	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Batura et al. [22]	Yes	N/A	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Include
Chernyak and Salamon [23]	Yes	N/A	Yes	No	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Ciani et al. [19]	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Cicione et al. [18]	Yes	N/A	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Constantinides et al. [12]	Yes	N/A	Yes	No	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Gugliotta et al. [20]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Lipovac et al. [13]	Yes	N/A	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Raymond et al. [14]	Yes	N/A	Yes	No	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Stalenhoef et al. [15]	Yes	N/A	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	Yes	Include
Torella et al. [17]	Yes[a]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Include

[a]Had three exposure groups

[b]Not available (N/A) because the two groups were the same participants (pre- vs post-treatment)

aminoglycoside owing to culture resistance to gentamicin at baseline (amikacin (1) and tobramycin (2)) without comments on their effectiveness. Further exploration of the efficacy of these IVA therapies through larger cohort or randomized controlled trials may broaden the scope of these treatments, especially when IVA gentamicin or HA + CS cannot be utilized.

Additionally, almost all of the studies included enrolled women in whom antibiotic therapy courses originally failed. However, most studies did not specify the number of failed courses before utilizing IVA therapy. Further research on defining the ideal candidates for IVA after oral antibiotics would help clinicians interested by this treatment modality in real life practice. Furthermore, although the majority of studies followed a weekly instillation schedule, the Stalenhoef et al. study reported a daily instillation schedule for the first 2 weeks. Further research exploring different administration intervals is therefore needed.

Recurrent UTIs are associated with creating a clinical, personal, and economic burden of illness [37]. Therefore, there is a need to explore the benefits of IVA therapy beyond reduction in rUTI rates. IVA therapy has been able to improve sexual dysfunction and other quality-of-life symptoms related to rUTIs [38]. A systematic review by Goddard and Janssen included three studies that used the pelvic pain and urgency/frequency (PUF) assessment tools to report on symptom change. The mean change in PUF score was −6.55, with the lower and upper scoring limits being 0 to 36 [39]. Therefore, there is a need to explore the benefits of IVA therapy beyond a reduction in rUTI rates.

Conclusions

In this review with a limited number of IVA studies on uncomplicated rUTIs, predominantly in women, instillations of gentamicin and hyaluronic acid with chondroitin sulfate had efficacy in the treatment of rUTIs when oral antibiotics had failed. Dosages of 80 mg of gentamicin per instillation and both 40 mg and 800 mg of hyaluronic acid were used effectively with limited adverse effects and short-term benefits. These encouraging findings should stimulate further research into the optimal modality of IVA instillation and into better defining ideal candidates for this bladder-targeted therapy.

Contributions M. Reddy: project development, data collection, and manuscript writing/editing; P.E. Zimmern: project development, data collection, and manuscript writing/editing.

Funding No funds, grants, or other support was received.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest None.

Ethics approval All procedures performed in this study were carried out in accordance with the ethical standards of the institutional research committee (UT Southwestern IRB) and with the 1964 Declaration of Helsinki and its later amendments.

References

1. Osamwonyi B, Foley C. Management of recurrent urinary tract infections in adults. Surgery (Oxford). 2017;35:299–305.
2. Malik RD, Wu YR, Zimmern PE. Definition of recurrent urinary tract infections in women: which one to adopt? Female Pelvic Med Reconstr Surg. 2018;24:424–9.
3. Glover M, Moreira CG, Sperandio V, et al. Recurrent urinary tract infections in healthy and nonpregnant women. Urol Sci. 2014;25:1–8.
4. Neugent ML, Hulyalkar NV, Nguyen VH, et al. Advances in understanding the human urinary microbiome and its potential role in urinary tract infection. mBio 2020;11:e00218-20.
5. De Nisco NJ, Neugent M, Mull J, et al. Direct detection of tissue-resident bacteria and chronic inflammation in the bladder wall of postmenopausal women with recurrent urinary tract infection. J Mol Biol. 2019;431:4368–79.
6. Sihra N, Malde S, Greenwell T, et al. Management of recurrent urinary tract infections in women. J Clin Urol. 2020;https://doi.org/10.1177/2051415820939456
7. Sharma S, Raison N, Ahmed K, et al. Antibiotic sparing approaches to treating rUTI: A systematic review. J Urol. 2020. https://www.ics.org/2019/abstract/530.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178–89.
10. 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.
11. 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.
12. 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.
13. Lipovac M, Kurz C, Reithmayr F, et al. Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. Int J Gynaecol Obstet. 2007;96:192–5.
14. Raymond I, Vasdev N, Ferguson J, et al. The clinical effectiveness of intravesical sodium hyaluronate (cystistat®) in patients with interstitial cystitis/painful bladder syndrome and recurrent urinary tract infections. Curr Urol. 2012;6:93–8.
15. Stalenhoef JE, van Nieuwkoop C, Menken PH, et al. Intravesical gentamicin treatment for recurrent urinary tract infections caused by multidrug resistant bacteria. J Urol. 2019;201:549–55.

16. Torella M, Del Deo F, Grimaldi A, et al. Efficacy of an orally administered combination of hyaluronic acid, chondroitin sulfate, curcumin and quercetin for the prevention of recurrent urinary tract infections in postmenopausal women. Eur J Obstet Gynecol Reprod Biol. 2016;207:125–8.
17. Torella M, Schettino MT, Salvatore S, et al. Intravesical therapy in recurrent cystitis: a multi-center experience. J Infect Chemother. 2013;19:920–5.
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. 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.
20. 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.
21. Abrams P, Hashim H, Tomson C, et al. The use of intravesical gentamicin to treat recurrent urinary tract infections in lower urinary tract dysfunction. Neurourol Urodyn. 2017;36:2109–16.
22. Batura D, Warden R, Hashemzehi T, et al. Intravesical sodium hyaluronate reduces severity, frequency and improves quality of life in recurrent UTI. Int Urol Nephrol. 2020;52:219–24.
23. Chernyak S, Salamon C. Intravesical antibiotic administration in the treatment of recurrent urinary tract infections: promising results from a case series. Female Pelvic Med Reconstr Surg. 2020;26:152–4.
24. Anger J, Lee U, Ackerman AL, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol. 2019;202:282–9.
25. Madersbacher H, van Ophoven A, van Kerrebroeck PE. GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans—a review. Neurourol Urodyn. 2013;32:9–18.
26. Van Nieuwkoop C, den Exter PL, Elzevier HW, et al. Intravesical gentamicin for recurrent urinary tract infection in patients with intermittent bladder catheterisation. Int J Antimicrob Agents. 2010;36:485–90.
27. Hurst RE, Van Gordon S, Tyler K, et al. In the absence of overt urothelial damage, chondroitinase ABC digestion of the GAG layer increases bladder permeability in ovariectomized female rats. Am J Physiol Renal Physiol. 2016;310:F1074–80.
28. Rozenberg BB, Janssen DAW, Jansen CFJ, et al. Improving the barrier function of damaged cultured urothelium using chondroitin sulfate. Neurourol Urodyn. 2020;39:558–64.
29. Fenner A. Intravesical hyaluronic acid and chondroitin reduces incidence of recurrent UTI. Nat Rev Urol. 2011;8:178.
30. Redorta JP, Sanguedolce F, Pardo GS, et al. Multicentre international study for the prevention with iAluRil of radio-induced cystitis (MISTIC): a randomised controlled study. Eur Urol Open Sci. 2021;26:45–54.
31. Physician fee schedule, Centers for Medicare & Medicaid Services, 2021.
32. iAluRil Prefill, iAluRIl, 2021.
33. Gaitonde S, Malik RD, Zimmern PE. Financial burden of recurrent urinary tract infections in women: a time-driven activity-based cost analysis. Urology. 2019;128:47–54.
34. Pietropaolo A, Jones P, Moors M, et al. Use and effectiveness of antimicrobial Intravesical treatment for prophylaxis and treatment of recurrent urinary tract infections (UTIs): a systematic review. Curr Urol Rep. 2018;19:78.
35. Wood GC, Chapman JL, Boucher BA, et al. Tobramycin bladder irrigation for treating a urinary tract infection in a critically ill patient. Ann Pharmacother. 2004;38(7-8):1318–9.
36. Dutta S, Lane F. Intravesical instillations for the treatment of refractory recurrent urinary tract infections. Ther Adv Urol. 2018;10:157–63.
37. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019;11:1756287219832172.
38. Nightingale G, Shehab Q, Kandiah C, et al. The effect of intravesical instillations with hyaluronic acid on sexual dysfunction in women with recurrent urinary tract infections (RUTI). Eur J Obstet Gynecol Reprod Biol. 2018;221:105–8.
39. Goddard JC, Janssen DAW. Intravesical hyaluronic acid and chondroitin sulfate for recurrent urinary tract infections: systematic review and meta-analysis. Int Urogynecol J. 2018;29:933–42.