# A Randomized Controlled Trial Comparing a New D-Mannose-based Dietary Supplement to Placebo for the Treatment of Uncomplicated *Escherichia coli* Urinary Tract Infections

*Stefano Salvatore* [a,b], *Alessandro Ferdinando Ruffolo* [a,b,*], *Guglielmo Stabile* [c], *Arianna Casiraghi* [a,b], *Gabriella Zito* [c], *Francesco De Seta* [c]

[a] *School of Medicine, Vita-Salute San Raffaele University, Milan, Italy;* [b] *Obstetrics and Gynecology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [c] *Department of Medical, Surgical and Health Sciences, Institute for Maternal and Child Health, University of Trieste, IRCCS Burlo Garofolo, Trieste, Italy*

## Abstract

***Background:*** The rise in antimicrobial resistance means that alternative approaches for the treatment and prevention of urinary tract infection (UTIs) are required.
***Objective:*** To evaluate the safety and efficacy of a D-mannose-based dietary supplement (D-mannose, citric acid, prebiotic fibers, *Astragalus*, and dandelion; DAPAD complex) for the treatment of uncomplicated acute *E. coli* UTIs.
***Design, setting, and participants:*** This was a single-center, randomized, double-blind, placebo-controlled trial conducted from April 2021 to October 2021 in Rajalakshmi Hospital and Research Centre (Bangalore, India). The participants were nonmenopausal women with an acute uncomplicated *E. coli* UTI. UTI was diagnosed according to the presence of at least one urinary symptom and bacteriuria (>100 000 CFU/ml).
***Intervention:*** The DAPAD complex was administered twice a day for 5 d, with phenazopyridine and alkalizing agents as the standard of care (SOC). The control group received placebo with SOC.
***Outcome measurements and statistical analysis:*** Subjective (clinical resolution/response) and objective (midstream bacteriuria) outcomes were evaluated at the end of therapy (day 6) and at day 35 of follow-up. Adverse events were recorded. Categorical variables were analyzed using $\chi^2$ and Fisher's exact tests; a $p$ value <0.05 was considered significant.
***Results and limitations:*** Seventy women were enrolled and equally randomized to the two groups. Clinical resolution was higher in the DAPAD group at 6 d (34.3% vs 0%; $p < 0.0001$) and 35 d from baseline (88.6% vs 20%, $p < 0.0001$). At day 35, no patients in the DAPAD group had moderate or severe symptoms, whereas 25.7% (nine/35) and 11.4% (four/35) of patients in the placebo group had moderate and severe symptoms, respectively. Bacteriological resolution was also higher in the DAPAD group at day 6 (85.7% vs 14.3%; $p < 0.0001$) and day 35 (100% vs 40%; $p < 0.0001$). Three mild adverse events (4.26%) unrelated to the investigated product were recorded, all of which were medically treated.
***Conclusions:*** The DAPAD complex dietary supplement is effective and safe for treatment of acute uncomplicated *E. coli* UTIs.

* Corresponding author. Obstetrics and Gynecology Unit, IRCCS San Raffaele Scientific Institute, San Raffaele Hospital, Via Olgettina 60, Milan, Italy. Tel. +39 393 148 2744.
E-mail address: alesruffolo@gmail.com (A.F. Ruffolo).

## 1. Introduction

Urinary tract infection (UTI) is a collective term denoting an infection that involves any part of the urinary tract. UTIs are one of the most common infections reported in local primary care. Adult women are 30 times more likely than men to develop a UTI, principally in subjects younger than 50 yr. Appropriate classification of UTI as a simple or complicated form guides its management, and the diagnosis is strictly related to identification of individual risk factors for UTIs according to the ORENUC (O-NO = known factors; R = risk of recurrent UTI; E = extra urogenital risk factors; N = nephropathy; U = urological risk factors that can be resolved by therapy; C = catheter) classification [1]. Family physicians can manage most UTIs when guided by patient history, laboratory analysis, and appropriate use of antibiotics to minimize antibiotic resistance [2]. While simple uncomplicated cystitis responds optimally to oral antibiotics, complicated UTIs may require early imaging, referral to the emergency department, or hospitalization to prevent urosepsis. *Escherichia coli* remains the predominant uropathogen in acute, community-acquired, uncomplicated UTIs.

UTIs result in considerable economic and public health burdens and significantly affect the quality of life (QoL) of afflicted individuals [3]. Currently, antibiotics such as trimethoprim sulfamethoxazole, ciprofloxacin, and ampicillin are the therapeutics most commonly recommended for UTIs [3]. However, the rise in antibiotic resistance and high recurrence rates threaten to greatly increase the burden of these common infections on health care systems.

The inexorable rise of antimicrobial resistance reinforces the need for alternative approaches for both treatment and prevention of UTIs, which include the use of novel vaccine (s), probiotics, and immunostimulants [4]. Among others, a potential therapeutic approach using D-mannose, an inert monosaccharide that is metabolized and excreted in urine and acts by inhibiting bacterial adhesion to the urothelium. Some studies have investigated the effect of D-mannose on recurrent UTIs (rUTIs) and as prophylaxis for UTIs. However, appraisal of this evidence remains under-reported.

The aim of our study was to evaluate the safety and efficacy of a dietary supplement containing D-mannose, citric acid, prebiotic fibers, *Astragalus*, and dandelion (DAPAD complex) for the treatment of acute uncomplicated *E. coli* UTI in the lower urinary tract.

## 2. Patients and methods

### 2.1. Study design

This was a randomized, prospective, double-blind, two-arm, parallel assignment, placebo-controlled trial to evaluate the efficacy and safety of a D-mannose-based dietary supplement (DAPAD complex developed by International Health Science srl, Milan, Italy) as an adjuvant therapy in the treatment of acute uncomplicated UTIs. The study was conducted at the Rajalakshmi Hospital and Research Centre (Bangalore, India) from April 2021 to October 2021.

Inclusion and exclusion criteria for the study population are reported in Table 1. Each patient included in the study participated in four study visits, including a screening visit (visit 0), a randomization visit (visit 1), an end-of-therapy visit at 6 d from randomization (visit 2), and a follow-up visit at 35 ± 5 d from randomization (visit 3).

The primary outcome of the study was the clinical response at the end of treatment (day 6) and 1 mo after the end of therapy (35 d). The primary outcome was defined as (1) clinical resolution (complete resolution of symptoms without prior failure) or (2) a clinical response (improvement of symptoms from a more severe to a less severe category). A secondary outcome was bacteriological resolution at the end of therapy (day 6), defined as eradication of the infecting *E. coli* strain (bacterial load $<10^5$ CFU/ml), with no recurrence of bacteriuria at 35-d follow-up.

### 2.2. Procedures

At the screening visit, the study procedures were explained during the informed consent session. Demographic characteristics (date of birth, sex, height, weight) and medical history were recorded. Medications for current or prior disease conditions (for a duration of 3 mo before the study start) were recorded. Vital parameters were recorded and a physical examination, including gynecological assessment, was performed. The following laboratory analyses were conducted: urine analysis (routine and microscopic examination); a urinary pregnancy test; and a urine culture and sensitivity test (midstream urine). The inclusion and exclusion criteria for subject eligibility were assessed.

Acute UTI was diagnosed according to the presence of at least one of the four lower urinary tract symptoms (LUTS) required for inclusion and a positive urine culture ($\geq 10^5$ CFU/ml). The terminology used to define urinary symptoms complies with the International Urogynecological Association and the International Continence Society standardization document [5]. Midstream urine samples were taken after washing the genital area with sterile water wipes after not voiding for at least 3 h before sample collection.

At visit 1, participants were randomized to the experimental group (DAPAD) or the control group (placebo) in a 1:1 allocation ratio. Because this was a double-blind study, neither the participants nor the clinicians involved in the trial had access to the randomization list. The study product (DAPAD or placebo) was dispensed to the participants with instructions on dosage and frequency. Study questionnaire assessments evaluating the severity of UTI symptoms were administered. All subjects were encouraged to report any incidence of adverse events (AEs).

At visit 2 and visit 3, the clinical response and bacteriological response were assessed. Questionnaires with the following questions were administered: "Have there been any changes in your UTI symptoms since the last visit?" and "If the answer is better, please indicate how much better".

At visit 3, the same laboratory tests as for the screening visit were evaluated.

**Table 1 – Inclusion and exclusion criteria for the study population**

| Inclusion criteria | Exclusion criteria |
|---|---|
| 1. Adult female of fertile age | 1. Male sex |
| 2. Age ≥18 yr to 45 yr | 2. Urine culture positive for uropathogens other than *E. coli* |
| 3. Written informed consent | 3. Pregnancy or planned pregnancy |
| 4. At least one of four key UTI symptoms that could be attributed to an uncomplicated UTI, and no alternative explanation (ie, symptoms suggestive of STI or vulvovaginitis): | 4. Concomitant antimicrobial therapy at the time of screening |
| • Dysuria | 5. Use of any antibiotics in the previous 7 d |
| • Urgency (including nocturia) | 6. Dietary supplements (such as cranberry, probiotics) during the month before recruitment |
| • Frequency | 7. Known or suspected hypersensitivity or allergy to any ingredient of the investigational product |
| • Suprapubic tenderness | 8. Active upper UTI (eg, pyelonephritis, urosepsis: fever >38.0 °C, flank pain, chills) |
| 5. Urine culture positive for *E. coli* $\geq 10^5$ CFU/ml | 9. Symptoms/signs suggestive of vaginitis or STI |
| | 10. Indwelling catheter, nephrostomy, ureteric stent, or other foreign material |
| | 11. Otherwise complicated UTI: |
| | • History of anatomic or functional abnormality of the urogenital tract: |
| | • Congenital abnormalities |
| | • Polycystic kidney disease |
| | • Obstruction or stricture of the renal pelvis, ureter, or urethra |
| | • Kidney stones |
| | • Cystocele |
| | • Cystic diverticulae |
| | • Change in anatomic proportions (eg, after ureter implantation) |
| | • Chronic vesicourethral reflux |
| | • Neurogenic bladder |
| | 12. Severe chronic renal (creatinine clearance < 30 ml/min) or hepatic dysfunction |
| | 13. Diagnosis of diabetes |
| | 14. Immunosuppression: |
| | • Untreated human immunodeficiency virus infection |
| | • Use of high-dose systemic corticosteroids or other immunosuppressive medication |
| | • Chemotherapy |
| | • Treatment with radiation |
| | 15. Critical illness requiring intensive care |
| | 16. Planned surgery within the next 6 wk |
| | 17. Pelvic or gynecological surgery during the 6 mo before recruitment |
| | 18. Inability to take oral drugs |
| | 19. Participation in another prospective clinical trial |
| | 20. Previous enrolment in the proposed study |
| | 21. Inability to understand or to follow the study protocol |

*E. coli* = *Escherichia coli*; STI = sexually transmitted infection; UTI = urinary tract infection.

The incidence of AEs and serious AEs (SAEs, defined as AEs that led to death or to serious deterioration in the health of the subject) during the study period was recorded.

### 2.3. Study treatment

The product investigated is DAPAD complex, a dietary supplement containing D-mannose 2000 mg, prebiotics 1500 mg (polydextrose and acacia gum), arabinogalactan 140 mg, Axtragyl 100 mg (*Astragalus membranaceus* root extract), and dandelion 50 mg (*Taraxacum officinalis* extract) in sachets. DAPAD was administered along with the standard of care (SOC), decided for each subject individually according to their urine culture and sensitivity results (phenazopyridine [6] and alkalizing agents [7] were recommended for patients, along with advice to drink plenty of water). The DAPAD dosage is two sachets per day (morning and evening), dissolved in a glass of water (150 ml) and mixed adequately, administered for 5 d. Subjects in the comparator arm received two sachets a day (morning and evening) of the placebo dissolved in a glass of water (150 ml) along with the SOC for 5 d.

### 2.4. Statistical analysis

R version 4.1.2 (R Foundation for Statical Computing, Vienna, Austria) was used for statistical analysis. Continuous variables are reported as the mean and standard deviation and categorical variables as the frequency and percentage. Categorical variables were analyzed using a $\chi^2$ test and Fisher's exact test, as appropriate. A $p$ value of <0.05 was considered statistically significant.

The sample size was calculated considering an a priori difference of 35% in clinical resolution between the two study groups. For an $\alpha$ error of 0.05 and study power of 80%, the total number of patients to enroll in the study was calculated as 62 women (31 women for each treatment arm).

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws and regulations. The study was approved by the institutional review board in all investigative centers (clinical trial number BIAG-CSP-046).

## 3. Results

A total of 76 women were screened for inclusion in the study protocol. Six patients (six/76; 7.89%) did not meet the inclusion criteria and were excluded from enrollment. Therefore, 70 women were included in the study and were prospectively randomized to the two groups (35 patients for each arm). The mean age was 33.89 ± 7.63 yr in the DAPAD group and 33.46 ± 8.31 yr in the placebo group.

None of the participants reported a relevant medical or surgical history or any prior therapy or medication.

Table 2 shows that there were no statistically significant differences in baseline resistance to antibiotics between the groups according to culture and sensitivity tests.

The clinical responses to therapy are shown in Table 3. There was a significantly greater likelihood of achieving complete resolution of symptoms in the DAPD group in comparison to the placebo group ($p < 0.0001$) at both 6 d from baseline (34.3% vs 0%) and 35-d follow-up (88.6% vs 20%). Moreover, at 35-d follow-up, no patient in the DAPD group had moderate or severe symptoms, whereas 25.7% (nine/35) and 11.4% (four/35) of patients in the placebo group had moderate and severe symptoms, respectively. Bacteriological resolution was significantly higher ($p < 0.0001$) in the DAPD group, as shown in Table 4. Only 14.3% (five/35) of patients in the DAPD group (in comparison to 85.7% of the placebo group; $p < 0.0001$) had a positive urine culture at 6 d from baseline, and none of them had a positive urine culture (in comparison to 60.0% of the placebo group; $p < 0.0001$) at 35-d follow-up.

Answers to the questions "Has there been any change in your UTI symptoms from the last visit?" and "If the answer is better, please indicate how much better" are reported in Table 5. The results indicate a significantly greater improvement in urinary symptoms in the DAPAD group.

Patients without a response to the treatment or the placebo, according to a positive urine culture, received an antibiotic treatment according to the antibiogram.

The 4.26% (three/70) of patients who reported an AE (Table 6) were all treated with a pharmacological agent until complete resolution. No SAEs were reported.

## 4. Discussion

The aim of our study was to evaluate the safety and efficacy of a D-mannose-based dietary supplement as treatment for acute uncomplicated *E. coli* UTI in the lower urinary tract. Our data show that women randomized to the DAPAD group experienced significantly higher rates of clinical LUTS resolution and response than women in the placebo group. Moreover, the DAPAD group had a significantly higher bacteriological response in comparison to the placebo group, with complete resolution at 35-d follow-up.

Although extensively researched for hundreds of years, UTIs continue to represent the most common infectious disease in women, are a leading cause of morbidity, health-associated expenditure, and diminished QoL, and are an important social burden [2,3,8–12]. On the basis of clinical

**Table 2 – Incidence of baseline antibiotic resistance**

| Antibiotic | Patients with antibiotic resistance, *n* (%) | | *p* value |
|---|---|---|---|
| | Placebo | DAPADC | |
| Amikacin | 6 (17.14) | 5 (14.29) | 0.75 |
| Ampicillin | 30 (85.71) | 26 (74.29) | 0.75 |
| Ceftazidime | 30 (85.71) | 27 (85.71) | 0.35 |
| Ciprofloxacin | 24 (68.57) | 22 (62.86) | 0.61 |
| Gentamicin | 0 (0) | 1 (2.86) | 0.31 |
| Meropenem | 0 (0) | 1 (2.86) | 0.31 |
| Piperacillin/tazobactam | 0 (0) | 0 (0) | NA |
| Amoxycillin/clavulanic acid | 0 (0) | 1 (2.86) | 0.31 |
| Cefepime | 30 (85.71) | 26 (74.29) | 0.75 |
| Cefuroxime | 30 (85.71) | 28 (80.0) | 0.53 |
| Cotrimoxazole | 30 (85.71) | 27 (77.14) | 0.35 |
| Imipenem | 0 (0) | 0 (0) | – |
| Nitrofurantoin | 0 (0) | 0 (0) | – |
| Tigecycline | 0 (0) | 0 (0) | – |

DAPADC = D-mannose-based dietary supplement.

**Table 3 – Summary of clinical outcomes**

| Urinary symptom severity | DAPADC (*n* = 35) | Placebo (*n* = 35) | *p* value |
|---|---|---|---|
| Visit 1 (baseline), *n* (%) | | | 0.80 |
| No symptoms | 0 (0) | 0 (0) | |
| Mild symptoms | 0 (0) | 0 (0) | |
| Moderate symptoms | 15 (42.9) | 14 (40.0) | |
| Severe symptoms | 20 (57.1) | 21 (60.0) | |
| Visit 2 (6 d), *n* (%) | | | <0.0001 |
| No symptoms | 12 (34.3) | 0 (0) | |
| Mild symptoms | 21 (60.0) | 6 (17.1) | |
| Moderate symptoms | 2 (5.7) | 12 (34.3) | |
| Severe symptoms | 0 (0) | 17 (48.6) | |
| Visit 3 (35 d), *n* (%) | | | <0.0001 |
| No symptoms | 31 (88.6) | 7 (20) | |
| Mild symptoms | 4 (11.4) | 15 (42.9) | |
| Moderate symptoms | 0 (0) | 9 (25.7) | |
| Severe symptoms | 0 (0) | 4 (11.4) | |

DAPADC = D-mannose-based dietary supplement.

**Table 4 – Summary of bacterial resolution in terms of eradication of the infecting *Eschericia coli* strain with no recurrence of bacteriuria**

| Time | Positive midstream urine culture (>100 000 CFU/ml), *n* (%) | | *p* value |
|---|---|---|---|
| | DAPADC (*n* = 35) | Placebo (*n* = 35) | |
| Visit 1 (baseline) | 35 (100.0) | 35 (100.0) | |
| Visit 2 (6 d) | 5 (14.3) | 30 (85.7) | <0.0001 |
| Visit 2 (35 d) | 0 (0) | 21 (60.0) | <0.0001 |

DAPADC = D-mannose-based dietary supplement.

**Table 5 – Summary of responses to the questionnaire on the symptoms of urinary tract infection**

| Question | Patients, *n* (%) | | *p* value |
|---|---|---|---|
| | DAPADC (*n* = 35) | Placebo (*n* = 35) | |
| **Has been there any change in your UTI symptoms from the last visit?** | | | |
| Visit 2 | | | <0.0001 |
| About the same | 1 (2.9) | 26 (74.3) | |
| Better | 34 (97.1) | 9 (25.7) | |
| Visit 3 | | | <0.0001 |
| About the same | 0 (0) | 19 (54.3) | |
| Better | 35 (100) | 16 (45.7) | |
| **If the answer is "Better", indicate how much better** | | | |
| Visit 2 | | | <0.0001 |
| A very great deal better | 8 (23.5) | 0 (0) | |
| A great deal better | 20 (58.8) | 3 (33.3) | |
| A good deal better | 3 (8.8) | 3 (33.3) | |
| Moderately better | 3 (8.8) | 2 (22.2) | |
| Somewhat better | 0 (0) | 1 (11.1) | |
| Visit 3 | | | <0.0001 |
| A very great deal better | 21 (60.0) | 0 (0) | |
| A great deal better | 13 (37.1) | 3 (18.2) | |
| A good deal better | 1 (2.3) | 12 (75.0) | |
| Moderately better | 0 (0) | 1 (6.3) | |
| Somewhat better | 0 (0) | 0 (0) | |

DAPADC = D-mannose-based dietary supplement; UTI = urinary tract infection.

**Table 6 – Summary of all AEs reported in the safety population**

| Group | AE term | AEs, *n* (%) | AE severity | SAE | Treatment | Related to IP |
|---|---|---|---|---|---|---|
| Placebo | Gastritis | 1 (1.42) | Mild | No | Medical | No |
| DAPADC | Gastritis and nausea | 1 (1.42) | Mild | No | Medical | No |
| DAPADC | Gastritis and vomiting | 1 (1.42) | Mild | No | Medical | No |

AE = adverse event; SAE = serious AE; IP = investigated product; DAPADC = D-mannose-based dietary supplement.

and biochemical criteria, UTIs are classified as lower tract (cystitis) and upper tract (pyelonephritis) infections. Empiric antibacterial therapy depends on the severity of the disease (eg, uncomplicated vs complicated UTIs), the spectrum of possible pathogens, and local resistance patterns [13]. The most frequent pathogens involved are from the Enterobacterales order, mainly *E. coli* and *Klebsiella pneumonia* [14]. The ever-increasing frequency of multidrug-resistant Enterobacterales spp., even among community-acquired infections, plays a major role in antibacterial treatment outcomes [15].

As the prevalence of recurrence after a first episode of UTI has been reported as 25–50% in different analyses, depending on the diagnosis criteria and the methodology used for detection, there is growing concern regarding the adverse effects of classic antimicrobial treatment of acute UTIs and the recurrent use of prophylaxis [16–18]. Apart from antimicrobial resistance, prolonged antibiotic treatment (especially with fluoroquinolones, aminopenicillins, or cephalosporins) leads to disruption of the normal bacterial flora, defined as a "collateral damage" phenomenon, and to the development of *Clostridium difficile* infections, with increasing diffusion worldwide [19–21].

Against this background, there is a lot of interest in non-antimicrobial types of UTI treatment, including urinary antiseptics, urine pH changers, bacterial adherence inhibitors, immunity enhancers, probiotics, and vaccines [22–25]. The availability of such products on the pharmaceutical market is increasing, but adequate information on their exact role in prophylaxis for UTI or in the treatment of acute UTI episodes is elusive [26]. D-Mannose is a natural sugar that mimics the host uroepithelial receptors targeted by uropathogens. It is believed that D-mannose creates a non-stick surface on the bladder wall, as well as around the bacteria. The hypothesis is that the bacteria are then expelled via urination, thus preventing the bacterial growth that leads to an infection within the bladder or urinary tract [27]. A recent systematic review supports the view that D-mannose reduces rUTI incidence, improves bothersome urinary symptoms, and leads to a longer time between episodes of UTI recurrence, with amelioration of QoL as a result of these effects [28]. Therefore, the efficacy of D-mannose has mainly been evaluated as prophylaxis for women affected by rUTIs [29] and to a lesser extent for women affected by acute UTI. A 2022 Cochrane review did not observe a positive effect of D-mannose for UTI prophylaxis and highlighted the severe lack of randomized controlled trials (RCTs) testing the efficacy of D-mannose in a wide range of populations [30]. According to the authors, future research in this field requires, in the first instance, a single adequately powered RCT comparing D-mannose with placebo [30]. The different D-mannose doses used in the trials they evaluated meant that meta-analysis was not possible. Moreover, the optimal dose of D-mannose to achieve effective urinary levels has not been assessed. At present, the European Association of Urology guidelines indicate that D-mannose should be used in the context of clinical trials [28]. Our RCT, with its strict inclusion and exclusion criteria and simple design, seems to answer the question regarding the efficacy of D-mannose in UTI.

Our data confirm that DAPAD therapy for acute UTI in the lower urinary tract is not only effective but is also safe, as only three nonserious AEs were reported in the study, all of which resolved spontaneously and were categorized as mild in nature by the investigator. All three AEs were not reported to be related to the study products.

This study has several points of strength, principally the randomized, double-blind design. Moreover, we adopted strict inclusion and exclusion criteria and evaluated both objective and subjective outcomes. Even though we did not assess urinary symptoms using validated questionnaires, we used a Likert scale to assess the severity of LUTS in women affected by UTI. However, we acknowledge that the lack of an answer regarding worsening of symptoms to the question "Has there been any change in your UTI symptoms from the last visit" can be considered as a slight bias in our trial. As the primary aim of the study was to observe the efficacy and safety of the study product in the treatment of acute uncomplicated UTI, we did not evaluate the recurrence of UTI after 35 d of follow-up; lack of long-term outcomes can be considered a limitation of the study.

## 5. Conclusions

We can conclude from the results that the DAPAD complex dietary supplement is an effective and safe product for treatment of acute uncomplicated *E. coli* UTIs. Further studies are needed to evaluate longer follow-up periods and the efficacy in other conditions, such as rUTI.

***Author contributions***: Alessandro Ferdinando Ruffolo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design*: Salvatore, De Seta.
*Acquisition of data*: Stabile, Zito.
*Analysis and interpretation of data*: De Seta, Stabile.
*Drafting of the manuscript*: Ruffolo, Casiraghi.
*Critical revision of the manuscript for important intellectual content*: Salvatore.
*Statistical analysis*: Zito, Ruffolo.
*Obtaining funding*: De Seta.
*Administrative, technical, or material support*: Casiraghi.

*Supervision*: Salvatore.
*Other*: None.

***Financial disclosures:*** Alessandro Ferdinando Ruffolo certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** The study was sponsored and supported by International Health Science. The sponsor played a role in the design and conduct of the study.

***Acknowledgments*:** The authors thank Rachel C. Applefield for her help with the English language revision of this paper.

## References

[1] Bjerklund Johansen TE, Botto H, Cek M, et al. Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. Int J Antimicrob Agents 2011;38 (Suppl):64–70. https://doi.org/10.1016/j.ijantimicag.2011.09.009.
[2] Nickel JC. Management of urinary tract infections: historical perspective and current strategies: part 1—before antibiotics. J Urol 2005;173:21–6.
[3] Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol 2019;11:.
[4] Bonkat G, Bartoletti R, Bruyère F, et al. EAU guidelines on urological infections. Arnhem, The Netherlands: European Association of Urology; 2020.
[5] D'Ancona C, Haylen B, Oelke M, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn 2019;38:433–77.
[6] Petrov SB, Slesarevskaya MN, Chibirov KH, Topuzov ME, Kagan OF, Voronova EN. Efficiency and safety of phenazopyridine for treatment of uncomplicated urinary tract infection: results of multi-center, randomized, placebo-controlled, clinical study. Urologiia 2020;3:15–21.
[7] Barea BM, Veeratterapillay R, Harding C. Nonantibiotic treatments for urinary cystitis: an update. Curr Opin Urol 2020;30:845–52.
[8] Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269–84.
[9] Kranz J, Schmidt S, Lebert C, et al. The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients: part 1. Urol Int 2018;100:263–70.
[10] Tandogdu Z, Wagenlehner FM. Global epidemiology of urinary tract infections. Curr Opin Infect Dis 2016;29:73–9.
[11] Rădulescu A, Mădan V, Aungurenci A, et al. Antibiotic resistant urinary tract infections in an urology ward. Rom J Mil Med 2015;118:20–2.
[12] Zaha DC, Bungau S, Aleya S, et al. What antibiotics for what pathogens? The sensitivity spectrum of isolated strains in an intensive care unit. Sci Total Environ 2019;687:118–27.
[13] Vata A, Hunea IM, Dorneanu O, et al. Biochemical changes and risk factors in the prognosis of antibiotics susceptibility in urinary tract infections. Rev Chim Buchar 2019;70:1822–5.
[14] Mihai IF, Lacatusu G, Filip-Ciubotaru F, Dorobat C, Romanescu C, Manciuc C. Major trends in the microbial etiology of urinary tract infection. Glob Adv Res J Microbiol 2019;8:35–7.
[15] Miftode E, Dorneanu O, Leca D, et al. Antimicrobial resistance profile of E. coli and Klebsiella spp. from urine in the Infectious Diseases Hospital Iași. Rev Med Chir Soc Med Nat Iasi 2008;112:478–82, In Romanian.
[16] 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.
[17] 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.
[18] Geerlings SE. Clinical presentations and epidemiology of urinary tract infections. Microbiol Spectrum 2016;4(5):3. https://doi.org/10.1128/microbiolspec.UTI-0002-2012.
[19] Cătălina Luca M, Roșu F, Hurmuzache M, et al. Updates in the assessment of risk factors in Clostridium difficile infection in patients with infectious diseases. Farmacia 2016;64:112–5.
[20] Paterson DL. 'Collateral damage' from cephalosporin or quinolone antibiotic therapy. Clin Infect Dis 2004;38(Suppl 4):S341–5.
[21] Schito GC, Naber KG, Botto H, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents 2009;34:407–13.
[22] Scottish Intercollegiate Guidelines Network. Management of suspected bacterial urinary tract infection in adults. SIGN publication no. 88. Edinburgh, UK: SIGN; 2012. 2012.
[23] Glover M, Moreira CG, Sperandio V, Zimmern P. Recurrent urinary tract infections in healthy and nonpregnant women. Urol Sci 2014;25:1–8.
[24] Chwa A, Kavanagh K, Linnebur SA, Fixen DR. Evaluation of methenamine for urinary tract infection prevention in older adults: a review of the evidence. Ther Adv Drug Saf 2019;10:.
[25] Eells SJ, Bharadwa K, McKinnell JA, Miller LG. Recurrent urinary tract infections among women: comparative effectiveness of 5 prevention and management strategies using a Markov chain Monte Carlo model. Clin Infect Dis 2014;58:147–60.
[26] Ratiu MP, Purcarea I, Popa F, et al. Escaping the economic turn down through performing employees, creative leaders and growth driver capabilities in the Romanian pharmaceutical industry. Farmacia 2011;59:119–29.
[27] Zopf D, Roth S. Oligosaccharide anti-infective agents. Lancet 1996;347:1017–21.
[28] Kyriakides R. Role of D-mannose in the prevention of recurrent urinary tract infections: evidence from a systematic review of the literature. Eur Urol Focus 2021;7:1166–9.
[29] Kranjčec B, Papeš D, Altarac S. D-Mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol 2014;32:79.
[30] Cooper TE, Teng C, Howell M, et al. D-Mannose for preventing and treating urinary tract infections. Cochrane Database Syst Rev 2022;8:CD013608.