Oral D mannose in the prevention and treatment of recurrent urinary tract infections: A review

Daniele Porru,1 Annalisa De Silvestri,2 Edda Buffa,1 Catherine Klersy,3 Barbara Gardella,3 Arsenio Spinillo,3 Hussein Jallous1
1Department of Urology; 2Clinical Epidemiology and Biometrics Service, Scientific Directorate; 3Gynecology and Obstetric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Abstract

The results of several studies reveal that antibiotics may promote treatment resistance by causing alterations in the intestinal flora. The development of a gut reservoir of resistant bacteria promotes the development of UTIs through autoinfection. This review aims to address clinical reliability, efficacy and safety of long-term treatment with oral D mannose for the prevention of Recurrent Urinary Tract Infections (RUTI) in females. A comprehensive MEDLINE, Embase, Scopus and Cochrane search was performed for English language reports published before December 2018 using the term “recurrent urinary tract infections and D mannose" was carried out. We searched Medline, Embase, Scopus and the Cochrane Register of Controlled Trials from January 2010 to December 2018. Eligible studies did not include non-oral therapy, local (vaginal) treatment in women with recurrent UTIs. We identified eligible original articles. A few limitations of the review are the heterogeneity of the available studies, their different rational and aim, the assumption of D mannose for prophylaxis or treatment of recurrent UTIs. Oral D mannose performs well in the prevention of UTIs recurrences, significant improvement of urinary symptoms was observed, the disease-free time was longer in the groups of patients under prophylaxis with D mannose in comparison with control groups (no treatment, antibiotic prophylaxis, prophylaxis with Proanthocyanidin (PAC) etc. The review has limitations, as the studies are heterogeneous, the meta-analysis requires classifications that can also be arbitrary. Furthermore, single-arm studies are not included. Some of the authors found this evidence inconclusive, which results as a limitation of the study. D mannose prolonged the recurrence-free interval of recurrent UTIs, thus reducing the prolonged or cyclical use of antibiotics, improving clinical symptoms, with a significant difference between treatment and control groups (no treatment, antibiotic prophylaxis, prophylaxis with Proanthocyanidin). However, most clinical trials used an association of different substances commingled with D mannose, dosages and regimens of D mannose were different. For this reason, the evidence of the efficacy of D mannose remains low.

Introduction

Rational

Approximately 25% of women with acute cystitis develop Recurrent Urinary Tract Infections (RUTI). The number of recurrences changes for each patient ranging between 0.3 and 7.6 episodes per year, UTI episodes often recurring with short intervals. Most RUTIs are caused by bacteria colonizing the faecal or periurethral reservoirs.1 A RUTI is commonly defined as more than two episodes of uncomplicated UTI in the last 6 months, or more than three in the last 12 months, documented by culture.2,3

Female patients who develop a UTI only 2 weeks from treatment for a UTI either have a new infection or have a recurrence of the infection caused by the initial uropathogen. The latter possibility is supported by cultures that grow the same species, particularly when it shares the same antimicrobial sensitivities. Prevention of UTIs has now become an important issue, Escherichia coli sequence type 131 (ST131), which is resistant to both fluoroquinolones and extended-spectrum beta-lactamases, has become responsible of an “invisible pandemic”, and realizes at least 80% of the uncomplicated outpatient urinary tract infections.4

Studies have shown antibiotics may promote treatment resistance by causing alterations in the gut flora. Promotion of the development of a gut reservoir of resistant bacteria enables UTIs to occur through autoinfection.5

Findings by Simmering and colleagues6 prompted the review of literature on Complementary and Alternative Medicine (CAM) therapies as a means to decrease hospitalizations and costs associated with RUTI.

Besides, women affected by RUTI are increasingly asking their healthcare professionals about the value of taking non-antimicrobial products.

In postmenopausal women with RUTI, L rhamnosus GR-1 and L reuteri RC-14 did not meet the non-inferiority criteria in the prophylaxis of RUTI in comparison to trimethoprim-sulfamethoxazole.7

In premenopausal women, Trimethoprim-sulfamethoxazole 480 mg once daily is more effective than cranberry capsules 500 mg twice daily to prevent recurrent UTIs.8

Ascorbic acid (vitamin C) cannot be recommended for the prevention of RUTI, cranberries contain proanthocyanidins that can inhibit adherence of P-fimbriated E. coli to the uroepithelial cell receptors. Cranberry compounds decrease RUTI about 30%-40% in premenopausal women with recurrent UTIs, however, their use proved to be less effective than low-dose antimicrobial prophylaxis, and besides, they are not recommended as a treatment option for UTIs.9 For this reason, we chose to review the results of oral D mannose over different natural compounds in patients with RUTI in all types of RUTI, not only E. coli RUTI.

D-mannose is a monosaccharide isomer of glucose, it contributes to glycosylation of specific proteins, such as monoclonal antibodies. Absorption of oral D-Mannose is quick, it can be detectable in the plasma.
about 30 minutes after assumption and it is finally excreted in the urinary tract.9

Similar findings of reduced bacteriuria levels emerged from in vivo animal UTI models.10-12 Besides, the positive correlation between a UTI infection history in first-degree female relatives and UTI risk suggests a genetic component for increased susceptibility.13 Recurrent UTIs are caused by E. coli in 80% of cases, Staphylococcus saprophyticus in 4.4%, Proteus mirabilis in 4.3%, Enterococcus faecalis in 3.2%, Klebsiella pneumoniae in 2.3%. Haemagglutination mediated by type 1 fim-briae of E. coli (Fim H) play an important role in its pathogenic activity.14

Although long-term antibiotics may reduce the risk of UTI recurrence in women, this benefit diminishes on cessation of treatment.15

D-mannose is a well-known sugar that has been extensively studied as a probiotic in vivo model.16 The anti-adhesive effect of mannose depends on the configuration of the molecule.17 The use of the estriol-containing vaginal pessary did not hinder new episodes of bacteriuria in women with RUTI in comparison to Nitrofurantoin Macrolactam (NM), prophylactic antimicrobial drugs, such as NM performed better for RUTI in postmenopausal women. The paper by Beerepoot et al.8 reports that in postmenopausal women with RUTI, L thamnosus GR-1 and L reuteri RC-14 do not satisfy the non-inferiority criteria in the prevention of UTIs when compared with trimethoprim-sulfamethoxazole. However, antibiotic resistance did not represent an issue in this group. In their systematic review Ahmed et al.18 report that antibiotic prophylaxis should be compared with non-antibiotic prophylaxis with some evidence of efficacy, although such aim remains an unmet need in clinical practice and research. They report that long-term antibiotics may reduce the risk of UTI recurrence in females, but the benefit stops when therapy is interrupted. Besides, there are potential damages from acquiring an antibiotic-resistant infection, thus the risk implied with long-term antibiotic use is an important factor to consider when establishing the choice of antibiotic prophylaxis.

In a recent pilot clinical trial9 two groups of 30 patients were treated, the first group received antibiotic first, and the second D-mannose first (Table 1). The crossover point was at 24 weeks in both groups A and B. Therefore patients in group A switched to group B at week 24, and vice versa. Data of patients in both groups who had a UTI and returned for at least one follow-up visit were included in the analysis of treatment outcome and adverse effects. A significant difference in the elapsed time to the onset of infection was found between patients on antibiotic treatment and those on treatment with D-mannose.

Kranjec et al.20 recently conducted a study in which after initial antibiotic treatment of acute cystitis 308 women with a history of RUTI and no other significant comorbidities were randomly allocated to three groups. The first group (n=103) received prophylaxis with 2 g of D-mannose powder in 200 mL of water daily for 6 months, the second (n=103) received 50 mg Nitrofurantoin daily, and the third (n=102) did not receive prophylaxis.

Patients in the D-mannose group and Nitrofurantoin group had a significantly lower risk of RUTI episodes during prophylactic therapy compared to patients in no prophylaxis group (60%). There was an absolute risk reduction of 45% compared to the control group. The difference between D-mannose and Nitrofurantoin group was not significant (5%). These results show that D-mannose may be useful for UTI prevention, the authors concluded that further clinical trials are needed to validate their conclusions.

In a recent randomized study by Domenici et al.21 D-mannose was administered twice daily for 3 days and subsequently once a day for 10 days in female patients with symptoms of acute cystitis (dysuria, frequency, urgency, suprapubic pain, nocturia, and hematuria) or asymptomatic with the diagnosis of UTI (defined as 10 3 or more colony-forming units –CFU – in 1 mL of clean voided midstream urine).

The authors report that after 15 days cultures performed resulted negative in 90.7% of patients (n = 39). Comparing baseline results of cultures, D mannose seemed to have had a significant positive effect on UTIs’ resolution (p = 0.0001). In this trial, the proposed scheme of administration as a prophylactic agent after treatment of an acute episode is once a day for one week every other month for 6 months.

The method of cyclic, discontinuous administration might have jeopardized the benefits obtained by this group of patients. Besides, backache and hematuria do not usually have the same relation with the severity of infection such as fever and lumbar tenderness, since in these cases, antibiotic therapy becomes both necessary and irreplaceable.

A prospective single-site open-label feasibility study by Phe’ et al. recruited 22 patients with Multiple Sclerosis (MS) with micturition symptoms reporting RUTI.22 Patients were administered D-mannose powder (Nature supplies, D-Mannose Ltd., Co Durham, UK) 1.5 g twice daily, for 16 weeks.

In this study the patients with MS experiencing RUTI and self-monitoring for
### Table 1 Clinical studies using D-mannose in recurrent urinary tract infections.

| Clinical trial | Agents used | Dose/ n. of administrations | Duration | N. of patients | Efficacy on RUTI | Side effects | Reference |
|----------------|-------------|-----------------------------|----------|----------------|------------------|--------------|-----------|
| Prospective randomized controlled study | D-mannose powder vs nitrofurantoin/therapy (A) | 2 g once daily | 6 months | 308 women | P<0.001 | Diarrhea 8% | Kranjcec et al. 2014 |
| Open | D-mannose + Lactobacilli + PACs 500 mg | 250 mg once daily (1 month), then twice daily (1 month) | 2 months | 35 women | Urinary p<0.001 improvement | UTI Symptoms assessment questionnaire (UTSA) | None reported | Vicariotto 2014 |
| Randomized cross-over trial | Oral d-mannose vs trimethoprim/sulfamethoxazole | 1 g 3 times/day (or 2 weeks, later 1g twice/day for 22 weeks | 24 weeks | 60 women | Longer TTR (Time To Recurrence) p<0.001 | None reported | Foru et al. 2014 |
| Prospective randomized vs no treatment | once a day for a week every other month | 6 months | 45 women | UTSA question, Dm, frequency, morbidities, resolution | P<0.001 | None reported | Domenici et al. 2016 |
| Prospective randomized study for Propylphane Orifas after urodynamic study | Proflavine 800 mg/day vs placebo | init 5 days regimen of oral 1000 mg D-mannose + 200 mg salicin 3 times a day followed by 7 days with 700 mg of D-mannose + 50 mg of Lactobacillus acidophilus. Maintenance (D-mannose plus La-14) was repeated at the same dosage for 15 days at each month for two months. | 3 months | 85 (45 women, 17 men); neurogenic and non-neurogenic patients | Frequency p<0.001 | None reported | Palleschi et al. 2018 |
| Multicenter randomized clinical trial | Nitrofurantoin (NIT) vs d-mannose | D-mannose + Lactobacilli + Salicin 3 times a day, | 3 months | 150 women | P<0.05 | None reported | Vicariotto 2014 |
| Open study | D-mannose + Salix + Lactobacillus acidophilus | once daily (produced release) | 24 weeks | 150 women | UTI recurrences p<0.5 | None reported | Domenici et al. 2016 |
| Multicenter randomized double-blind study | Mucosaq, D-mannose 2 g + PEC 10 mg + vit. C-E-A vs proanthocyanidine 240 mg | | 6 months | 60 women | Lower median bacterial load compared to baseline. | None reported | Del Popolo et al. 2018 |
| Clinical trial | Agents used | Dose/ n. of administrations | Duration | N. of patients | Efficacy on RUTI | Side effects | Reference |
| Double blind, prospective randomized three-arm parallel group trial | Berberine, atractylochin, birch + D-mannose 400 mg (A) or berberine, atractylochin, birch + d-mannose 420 mg (B) vs proanthocyanidine 240 mg 3 times a day. | once daily | 12 weeks | 72 women | <RUTI in group A and B vs. C (statistical significance not reported) | None reported | Genovese et al. 2018 |
| Observational retrospective clinical study | Naosol susp 100 mg + D-mannose 500 mg + Morinda citrifolia leaf extract 200 mg + antibiotic (group A) vs antibiotic alone: (group B) | 1 tablet every 12 h for 60 days and then 1 tablet every 24 h for 4 months. Antibiotic: fosfomycin 3 grams per day for 2 days, to be repeated every 15 days for a total of three cycles, nitrofurantoin 100 mg three times a day for 6 days and propranolol 1,000 mg or proflavine 600 mg 1 capsule/day for 6 days. | 6 months | 60 women | <RUTI in group A (statistical significance not reported) | Marchetti et al. 2017 |
| Open-label feasibility study | D-mannose powder | 15 g twice daily | 16 weeks | 22 women group I: multiple sclerosis (MS), no urodynamic testing (U.I.) | <number of monthly UTIs p<0.01 (group I), group 2: MS, no I.C. | | Phé et al. 2017 |
| Open study | D-mannose, H. sabdariffa, Lactobacillus plantarum Lp 115 | 100 female patients | 38% negative urine cultures | None reported | Mihailid et al. 2019 |
| Randomized parallel group intervention trial | Rosiprom 1 sachet UROFOS 800 mg plus group A UROFOS containing S&R PACs (200 mg) with type-A proanthocyanidines (17 mg), D-mannose 1000 mg, chondroitin sulfate (200 mg), vitamin C (120 mg) and hyaluronic acid (100 mg) group B: no treatment | 2 sachets for 2 weeks and one sachet for two more weeks. | 12 weeks | 40 women | Group A: lower incidence of episodes of RUTI during treatment and follow-up. Urine samples had a significantly lower median bacterial load compared to baseline. Lower incidence of positive urine cultures compared to group B. | None reported | Manno et al. 2018 |
infections took D-mannose, which was associated with a reduction in the number of UTIs, however, a statistically significant reduction of UTIs could not be demonstrated. Besides, particularly in patients using catheters, the specificity and positive predictive value of positive results for leukocyte esterase and nitrates for symptomatic and clinically relevant, UTI is low.

Genovese et al. conducted a randomized three-arm parallel-group intervention trial to evaluate the prophylactic effects of three plant-based oral formulations combined with d-mannose on female subjects with a history of RUTI presenting with uncomplicated cystitis.

The study included a total of 72 women with acute cystitis and a history of recurrent cystitis episodes. The authors observed an increase in the rate of bacteriuria in patients treated with proanthocyanidins and d-mannose during follow-up, on the other hand, berberine, arbutin, birch and forskolin in conjunction with d-mannose reduced the prevalence of positive urine cultures during the study period.

The difference in the results may be due to the acid urinary environment developed with the employment of proanthocyanidins, which appears to reduce the effectiveness of D mannose, requiring neutral or alkaline urine for its best effectiveness.

The study provides further evidence in support of the use of selected botanicals, including d-mannose, proving their potential for safe and effective control of RUTI.

Thirty-five premenopausal, non-pregnant women presenting acute uncomplicated cystitis were enrolled in a pilot study by Vicariotto et al. Eligible subjects were at least 18 years old and had active, uncomplicated cystitis diagnosed by urine dipstick testing and an evaluation of the presence of specific urinary symptoms. This study was conducted to assess the effectiveness of an association of a cranberry dry extract, a gelling complex composed of the exopolysaccharides produced by Streptococcus thermophilus ST10 (DSM 25246) and tara gum, as well as the 2 microorganisms Lactobacillus Plantarum LP01 (LMG P-21021), Lactobacillus para-casei LPC09 (DSM 24243), and a small dose of D mannose, 250 mg. Patients were treated with 2 doses per day for 1 month, the following treatment continued with a single dose, 250 mg, until the 60th day. Improvement was reported in scores related to 4 out of 5 symptoms. The association of cranberry, D mannose and lactobacilli decreased the number of recurrences recorded during the one-month follow-up. However, a proper judgment of D mannose cannot be provided with such a low dose. Besides, urine dipstick testing was used during the initiation of symptoms to diagnose UTI and to quantify the efficacy of the product tested, therefore a urine culture could not assess appropriately bacterial species and load.

A multicentric double-blind study by Salinas-Casado et al. evaluated Manosar, containing D mannose 2 gr-proanthocyanidins (PAC), 140 mg-ac. ursoic 7.98 mg-Vit. A, C, E versus PAC 240 mg, one sachet per day, in a female population with recurrent UTIs for 24 weeks. Ninety-three out of 150 female patients with recurrent UTIs were assigned to these 2 different prophylactic treatment schemes: Manosar or PAC 240 mg, both compounds had prolonged release. During the six months 1/3 of patients under 240 mg PAC, 1/4 of patients treated with Manosar and nearly 50% of patients receiving placebo had recurrent UTIs. A significant difference was found between treatment and placebo group, p<0.05, although the small number of patients in each prophylactic treatment group did not allow to compare results between Manosar and PACs.

De Leo et al. evaluated the use of a dietary supplement (Kistinox® Forte sachets) containing cranberry (Vaccinium macrocarpon), Noxamicina® (propolis extract) and D-mannose in the treatment of cystitis, with or without bacteriuria: a multicenter clinical study was performed on 150 women aged 40 to 50 suffering from recurrent UTIs for 24 weeks. Ninety-three out of 150 patients under antibiotic therapy of various types. The second group of 20 patients received antibiotic therapy according to antibiotic sensitivity. In the first group only 5 out of 40 patients, 12.5%, had a positive urine culture, while the rate was 90% in the group under antibiotic treatment. The results of this study, although encouraging in this specific and particular category of patients, may be greatly affected by concomitant systemic hormonal treatment required for breast cancer, therefore cannot be regarded as completely reliable.

Del Popolo et al. evaluated 78 patients, males and females, with recurrent bacterial cystitis who received an initial 5-days regimen consisting on an oral combination of 1000 mg of D-mannose plus 200 mg of dry willow extract (salicin) three times daily, followed by 7-days with 700 mg of D-mannose plus 50 mg (1x109 CFU) of Lactobacillus acidophilus (La-14) twice daily as maintenance treatment, morning and evening. The association D-mannose plus La-14 was repeated at the same dosage for 15-days at each month for two months. One group under evaluation had a neuropenic bladder, 37 of them were on intermittent catheterization regimen. In both groups with neurogenic and non-neurogenic bladder dysfunction, the improvements of clinical symptoms (e.g. dysuria, frequency, urgency) were already significant 2 weeks after starting treatment and these results were confirmed after the maintenance therapy and 1 month after the end of treatment. Urine cultures were not scheduled in the follow-up period to check the percentage of objective clearance from bacterial urinary infection.

A clinical trial that included 308 women >18 years of age with acute UTI and history of RUTI was performed, initial antibiotic treatment of the acute UTI was given, ciprofloxacin 500 mg twice daily for 1
week, thereafter patients were randomly allocated to three groups. The first was given prophylaxis with 2g of D mannose powder daily for 6 months, the second received prophylaxis with nitrofurantoin 50 mg once a day, and the third received no prophylaxis or treatment. The risk of RUTI episodes was significantly higher in the no-prophylaxis group in comparison to the groups that received active prophylaxis (relative risk 0.24 and 0.34). Patient compliance in the treatment group was high and there was no difference between patients taking nitrofurantoin or D-mannose.29

In 100 female consecutive patients undergoing a urodynamic invasive procedure, a phytotherapeutic product composed of D-mannose (1000mg), H. sabdariffa (200mg), and Lactobacillus Plantarum Lp-115 (1mld UFC) was prescribed after urodynamic invasive test.30 Urine culture was positive in 13% of patients, 3 patients were symptomatic, 10 had asymptomatic bacteriuria, the authors concluded that D mannose reduced the risk of bacteriuria and urinary tract infection in women after invasive urodynamic procedures.

Manno et al.31 performed a prospective comparative study, 40 women with UTI received a single sachet of Fosfomycin Tromethamine (3gr). Patients were then randomly assigned to two groups: Group A: 20 women were given a supplement containing cranberry extracts (S&R PACs), D-mannose, Hyaluronic Acid and Glucosamine Chondroitin, UROIALTM 2 sachet per day during the first 7 days, then 1 sachet per day for two weeks; Group B: 20 women forming a control group did not receive any treatment. A complete resolution of symptoms was reported in the majority (85%) of patients in Group A while only 10 % was reported by subjects in the untreated control group.

Statistical analysis
Heterogeneity is checked using the Chi2 test and the I-squared statistic.32 The criteria for identification of heterogeneity are P value less than 0.10 for the Chi-squared test and an I-squared statistic greater than 50%. When there is no statistical evidence for heterogeneity in effect sizes, we use the fixed-effect model33 to metanalyze RRs; when significant heterogeneity is identified, we use the random-effects model34 and explore sources of significant heterogeneity. Analyses are stratified distinguishing if D mannose was used alone or in combination.

Figure 1 reports Forest plot showing comparison of D mannose (alone or in combination) with no treatment, placebo or non antibiotic therapy in preventing UTI episode. Relative risk is 0.29 (95% CI 0.2-0.42) p<0.001 Overall heterogeneity is low (I2 31%).

Figure 2 reports Forest plot showing comparison of D mannose (alone or in combination) with antibiotic therapy in preventing UTI episode. Relative risk is 0.71 (95% CI 0.40-1.26) p=0.24. Overall heterogeneity is low (I2 0%).

Discussion
Most reviews have shown that antibiotic prophylaxis lasting from 6 to 12 months or longer significantly reduces the rate of bacterial recurrences in a female population with RUTI, however, no agreement exists on when to start the prophylaxis, when to stop it and how long it should be carried out, as well as which should be the appropriate class and dose of antibiotic treatment.

Several prophylactic antibiotic schemes have been used with similar clinical results. Usual clinical regimens were trimethoprim-sulfamethoxazole, trimethoprim alone, nitrofurantoin, cephalaxin and low-dose fluoroquinolones for 6 months. With long-
term antibiotic prophylaxis, adverse reactions were occasionally observed, additional downsides were costs, growing bacterial resistance to antibiotics; due to these reasons, alternative prophylactic compounds, such as cranberry juice, probiotics and other substances have been extensively studied.38

A single Centre Open-label Feasibility Study Evaluating the Use of D-mannose for prevention of UTIs in Multiple Sclerosis was registered in 2015 in ClinicalTrials.gov. Study arms are 2, both patients with spontaneous voiding and patients using urinary (urethral or suprapubic) catheter were recruited. Results are not available yet.32

In another trial women with a history of RUTI were followed for 6 months, and were randomized either to d- mannose powder, dispensed in 2 g neutral sticks, or to placebo. The primary objective of this prospective, randomized, double-blinded placebo-controlled study was to investigate if treatment with d-mannose reduces the risk for a UTI recurrence compared to treatment with placebo. No results are reported so far.33

The increasing prevalence of Uropathogenic Escherichia Coli (UPEC) resistant to last-line antibiotic treatments, including colistin and carbapenems, make UTIs a noticeable example of the antibiotic-resistance crisis and emphasize the need for new approaches to eliminate and prevent bacterial infections.34-36 UPEC strains act by creating reservoirs in the gut from which they spread through the faeces, can colonize the periurethral area or vagina and then colonize the urethra to the urinary tract, where they cause UTI.37

Several emerging therapies including D-mannose, probiotics and vaccination have become available for RUTI.

The study carried out by Salinas-Casado14 evaluating a single daily formulation of 2 g D mannose prolonged release, Manosar, represents an innovation. Most commercial products with D mannose should be taken repeatedly in the day since its efficacy is based on few studies usually including a low number of patients, using combinations of substances containing D mannose or non-randomized, occasionally including patients with non-homogeneous characteristics (neurologic and non-neurologic).

Significant adverse events were not reported in all studies examined.

In 2009 a scientific opinion on the substantiation of a health claim related to a Uroval® and urinary tract infection has been reported, the panel concluded that a cause and effect relationship has not been established between the consumption of the cranberry extract and D-mannose containing food supplement Uroval® and the reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract.39 However the claim relates specifically to Uroval, a combination of D mannose and cranberry extract. Since this report of more than 10 years ago, many more clinical trials with D mannose examined in this review have been performed.

Conclusions

Several alternatives to antibiotics exist which are currently being explored. Our review allowed us to record that D mannose helps to prolong the recurrence-free interval, and therefore reduce the prolonged or cyclical use of antibiotics. In most of the published clinical trials, an improvement in clinical symptoms was proved, a significant difference was found between treatment and placebo group or group treated with antibiotics. However, the majority of clinical trials used the association of different compounds commingled with D mannose, besides dosages and regimens of d-mannose were different. For this reason, the evidence of the efficacy of d-mannose remains low since its efficacy is based on few studies usually including a low number of patients, using combinations of substances containing D mannose or non-randomized, occasionally including patients with non-homogeneous characteristics (neurologic and non-neurologic).

References

1. Nosseir SB, Lind LR, Winkler HA. Recurrent uncomplicated urinary tract infections in women: a review. J Womens Health (Larchmt) 2012;21:347-54.
2. Epp A, Larochelle A, Lovatsis D, et al. Recurrent urinary tract infection. J Obstet Gynaecol Can 2010;32:1082–119.
3. Nosseir SB, Lind LR, Winkler HA. Recurrent uncomplicated urinary tract infections in women: a review. J Women's Health (Larchmt) 2012;21:347–54.
4. Lautenbach E. Editorial commentary: flying under the radar: the stealth pan- demic of Escherichia coli sequence type 131. Clin Infect Dis 2013;57:1266–9.
5. Bryce A. Comparison of risk factors for, and prevalence of, antibiotic resistance in contaminating and pathogenic urinary Escherichia coli in children in primary care: prospective cohort study. J Antimicrobial Chemother 2018;73:1359–67.
6. Simmering JE, Tang F, Cavanaugh JE, et al. The increase in hospitalizations for urinary tract infections and the associated costs in the United States, 1998–2011. Open Forum Infect Dis 2017;4:281.
7. Beerepoot MA, ter Riet G, Nys S, et al. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. Arch Intern Med 2011;171:1270-8.
8. Beerepoot MA, Geerlings S. Non-antibiotic prophylaxis for urinary tract infections. Pathogens 2016;5:E36.
9. Michaels EK, Chmiel JS, Plotkin BJ, Schaeffer AJ. Effect of D-mannose and D-glucose on Escherichia coli bacteriuria in rats. Urol Res 1983;11:97–102.
10. Harwalkar A, Gupta S, Rao A, Srinivasa H. Prevalence of virulence factors and phylogenetic characterization of uropathogenic Escherichia coli causing urinary tract infection in patients with and without diabetes mellitus. Soc Trop Med Hyg 2015;109:769-74.
11. Stapleton A, Nudelman E, Clausen H, et al. Binding of uropathogenic Escherichia coli R45 to glycolipids extracted from vaginal epithelial cells is dependent on histo-blood group secre- tor status. J Clin Investig 1992;90:965–72.
12. Scholes D, Hawn TR, Roberts PL, et al. Family history and risk of recurrent cystitis and pyelonephritis in women. J Urol 2010;184:564-9.
13. Costello C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096.
14. Salinas-Casado J, Méndez Rubio S, Esteban Fuertes M, et al. Eficacia y tolerancia terapèutica de la D-Manosa (2 g) en el manejo de infecciones urinarias. Revisión sistemática. Med Clin (Barc) 2009;132:816-22.
15. Forbes R, Ali A, Abouhajar A, et al. Alternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women (ALTAR): study protocol for a multicentre, pragmatic, patient-randomised, non-inferiority trial. Trials Biomed Central 2018;19:616.
16. Michaels EK, Chmiel JS, Plotkin BJ, Schaeffer AJ. Effect of D-mannose and D-glucose on Escherichia coli bacteriuria in rats. Urol Res 1983;11:97–102.

[Urogynaecologia 2021; 33:239]
17. Raz R, Colodner R, Rohana Y, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in post-menopausal women. Clin Infect Dis 2003;36:1362–8.

18. Ahmed H, Davies F, Francis N, et al. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. BMJ Open 2017;7:e015233.

19. Porru D, Parmigiani A, Tinelli C, et al. Oral D-mannose in recurrent urinary tract infections in women: a pilot study. J Clinical Urol 2014;7:208-13.

20. Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol 2014;32:79–84.

21. Domenici L, Monti M, Bracchi C, et al. D-Mannose: a promising support for acute urinary tract infections in women. A pilot study. Eur Rev Med Pharmacol Sci 2016;20:2920-5.

22. Phé V, Pakzad M, Haslam C, et al. Open label feasibility study evaluating D-mannose combined with home-based monitoring of suspected urinary tract infections in patients with multiple sclerosis. Neurourol Urodynamics 2017;36:1770–5.

23. Genovese C, Davinelli S, Mangano K, et al. Effects of a new combination of plant extracts plus d-mannose for the management of uncomplicated recurrent urinary tract infections. Jo Chemother 2018;30:107-14.

24. Vicariotto F. Effectiveness of an association of a cranberry dry extract, D-mannose, and the two microorganisms lactobacillus plantarum LP01 and lactobacillus paracasei LPC09 in women affected by cystitis a pilot study. J Clin Gastroenterol 2014;48:S96-S101.

25. De Leo V, Cappelli V, Massaro MG, et al. Evaluation of the effects of a natural dietary supplement of cranberry, noxamin® and d-mannose in recurrent urinary tract infections in peri-menopausal women. Minerva Ginecologica 2017;69:336-41.

26. Palleschi G, Carbone A, Zanello PP, et al. Prospective study to compare antibiosis versus the association of N-acetylcysteine, D-mannose and Morinda citrifolia fruit extract in preventing urinary tract infections in patients submitted to urodynamic investigation. Arch Ital Urol Androl 2018;94:26-50.

27. Marchiori D, Zanello PP. Efficacy of N-acetylcysteine, D-mannose and Morinda citrifolia to treat recurrent cystitis in breast cancer survivals. In Vivo 2018;32:1105-6.

28. Altarac S, Papes D. Use of d-mannose in prophylaxis of recurrent urinary tract infections (UTIs) in women. BJU Int 2018;119:931-6.

29. Milandri R, Maltagliati M, Bocchialini T, et al. Effectiveness of D-mannose, Hibiscus sabdariffa and Lactobacillus plantarum therapy in prevention of infectious events following urodynamic study. Urologia 2019;86:122-5.