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Oral D-Mannose in the Prevention and Treatment of Recurrent Urinary Tract Infections: A Review

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Abstract

Background: 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. The aim of this review is to address clinical reliability, efficacy and safety of long-term treatment with oral D-Mannose for the prevention of Recurrent Urinary Tract Infections (RUTIs) in females.

Materials and Methods: Evidence Acquisition 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." We searched Medline, Embase, Scopus and the Cochrane Register of Controlled Trials since January 2010 to December 2018. Eligible studies did not include non-oral therapy, local (vaginal) treatment in women with RUTIs. We identified eligible original articles. The heterogeneity of the available studies, their different rationale and aim, the assumption of D-mannose for prophylaxis or treatment of recurrent UTIs need to be taken into account.

Results: Evidence Synthesis 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.

Conclusion: D-mannose prolonged the recurrence-free interval of recurrent UTIs, thus reducing the prolonged or cyclical use of antibiotics, generating an improvement of clinical symptoms, with a significant difference between treatment and control groups (no treatment, antibiotic prophylaxis, prophylaxis with Proanthocyanidin). However, the majority of 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 efficacy of D-mannose remains low.

Keywords: Recurrent urinary tract infections; Urinary tract infections; D-mannose; Antibiotic prophylaxis; Proanthocyanidin

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Introduction

Rationale

Approximately 25% of women with acute cystitis develop Recurrent Urinary Tract Infections (RUTI) [1]. 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 RUTI are caused by bacteria colonizing the fecal 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 a development of a gut reservoir of resistant bacteria enables UTIs to occur through autoinfection [5]. Findings by Simmering and colleagues [6] prompted to review 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-antibiotic 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 RUTI [7]. 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% to 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 [8]. For these 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 min 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]. RUTI 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* iL 2.3%. Haemagglutination mediated by type 1 fimbriae of *E. coli* (Fim H) play an important role in its the 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 structure is similar to the binding site of urothelial glycoprotein receptors, thus it acts as a competitive inhibitor of bacterial adherence; when an adequate concentration is reached in urine, D-mannose causes saturation of FimH adhesins and prevents the bacteria from attaching to urothelial receptors. A reduction of bacteriuria levels has been found *in vivo* animal UTI models [16], the anti-adhesive effect of mannose depends on the configuration of the molecule.

Objectives

The aim of the current study is to review the available literature data to identify the role and compare the results of different orally administered preparations having in common the use of d mannose in different dosages, alone or in combination with different, potentially synergistic compounds, for prevention and treatment of RUTI.

Evidence Acquisition

A non-systematic literature search of the Medline, Embase, Scopus and Cochrane Library databases was performed screening all the articles indexed in the aforementioned databases from January 2010 up to December 2018 using the following keywords or mesh terms: "urinary tract infections, D-mannose prophylaxis, antibiotic prophylaxis, antibiotic resistance, UTI, treatment, prevention" from January 2010 to December 2018 using medical subject headings. After screening manuscripts based on the title and abstract, full text evaluation of the remaining articles was done. We considered clinical trials, prospective studies, retrospective studies and comparative series concerning the evaluation of d mannose in RUTI. Studies assessing the comparison of results of different types of antibiotics or different antibiotic dosages or schemes were excluded; trials reported with awaited results were not part of the evidence synthesis.

Search strategy and selection criteria

Only publications with the text and/or the abstract written in the English language were considered. Additional papers cited in the references of the search manuscripts were further examined. Our literature search identified 15 articles pertaining to the search terms (Word variations have been searched). Further analysis of these articles resulted in 11 clinical trials which were deemed relevant to our review. The retrieved studies were assessed for their relevance based on the title and abstracts. Finally, studies references were screened in order to identify eventually unknown studies.

Evidence Synthesis

The use of the estriol-containing vaginal pessary [17] did not hinder new episodes of bacteriuria in women with RUTI in comparison to Nitrofurantoin Macrocrystal (NM), prophylactic antimicrobial drugs, such as NM performed better for RUTI in postmenopausal women. The paper by Beerepoot reports that in postmenopausal women with RUTI, L rhamnosus 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 [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 trial [19] two groups of 30 patients were treated, the first group received antibiotic first and the second D-mannose first (Table 1). The cross-over 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 symptomatic 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 an infection was found between patients on antibiotic treatment and those on treatment with D-mannose. Kranjcec [20] recently conducted a study in which after initial antibiotic treatment of acute cystitis 308 women with 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 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 [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, supra-pubic pain, nicturia, and hematuria) or asymptomatic with 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 with 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 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 patient with MS experiencing RUTI and self-monitoring for 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 nitrites for a symptomatic and clinically relevant, UTI is low. Genovese [23] 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 a safe and effective control of RUTI. Thirty-five premenopausal, non-pregnant women presenting acute uncomplicated cystitis were enrolled in a pilot study by Vicariotto [24]. 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 paracasei* 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 60^{th} 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 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 evaluated Manosar, containing d mannose 2 gr. Proanthocyanidins (PAC), 140 mg-ac. ursolico 7.98 mg- Vit. A, C, E *vs.* PAC 240 mg, one sachet per day, in a female population with recurrent UTIs for a period of 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 released. During the six-month period 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 [25] 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 RUTI, confirmed by a positive urine culture during the six months preceding their recruitment. Patients were randomly assigned to 2 groups of treatment, 100 women were given Kistinox® Forte, 1 sachet per day during the first 10 days of the month, for 3 months; in the second group 50 women served as a control group and received no treatment.

The authors report that a complete remission of urinary symptoms was observed in 92 women; a slight decrease in urinary symptoms was observed in 5 subjects. In this study the dose of d mannose contained in the treatment group is not indicated, the method/scale used for measurement of symptomatic change was not specified, and the recurrence rate in each group as well as the time to recurrence, a parameter of great importance, was not disclosed.

Palleschi [26] recruited 80 patients eligible for urodynamic examination, 42 men and 38 women, they were randomized to two groups, the former received antibiotic therapy with oral Prulifloxacine 400 mg/day for 5 days, the latter received an association of d mannose 500 mg- N-acetylcysteine (NAC)- Morinda Citrifolia fruit extract, two vials/day for 7 days. Ten days after the urodynamic study patients were submitted to urine examination and urine culture.

Results

The follow up assessment didn't show statistical significant difference between the two groups regarding the incidence of UTI. This study has a slightly different prospective, its intent is not treatment of UTIs episodes, but evaluation of preventive activity on UTIs following a urologic invasive diagnostic procedure such as urodynamic investigation. A recent retrospective clinical study [27] evaluated 60 patients affected by breast cancer with RUTI; they were on hormonal adjuvant therapy. Forty out of 60 were treated with d mannose 500 mg- n-acetylcysteine 100 mg- Morinda citrifolia fruit extract 200 mg every 12 h for 8 weeks, then once a day for 4 months, associated with antibiotic therapy of various types. A 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

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/ no treatment	2 g once daily	6 months	308 women	p<0.001	diarrhea 8%	Kranjčec et al. [19]
open	d mannose + *Lactobacilli* + PACs 500 mg	250 mg, once daily (1 month), then twice daily (1 month)	2 months	35 women	unclear p<0.001 improvement UTI Symptoms Assessment questionnaire (UTISA)	none reported	Vicariottto et al. [23]
randomized cross-over trial	oral d-mannose *vs.* trimethoprim/ sulfamethoxazole	1 g, 3 times/day for 2 weeks, later 1 g twice/day for 22 weeks	24 weeks	60 women	longer TTR (Time To Recurrence) p<0.0001	none reported	Porru et al. [18]
prospective randomized	*vs*., no treatment	once a day for a week every other month	6 months	45 women	UTISA question. dysuria, frequency, urgency UTIs resolution p<0.0001		Domenici et al. [20]
prospective randomized study for prophylaxis of UTIs after urodynamic study	prulifloxacine 400mg/day *vs.* vials of Ausilium NAC (D-mannose 500 mg, N-acetylcysteine 100 mg and Morinda citrifolia fruit extract 300 mg)	vials twice/day	7 days	80 (42 men, 38 women)	no difference between prulifloxacine and Ausilium NAC	none reported	Palleschi et al. [25]
multicenter randomized clinical study	Kistinox Forte (cranberry Noxamicina, D-mannose) *vs.* no treatment	Kistinox Forte 1 sachet/day the first 10 days of the month	3 months	150 women	p<0.05	none reported	De Leo et al. [24]
open study	D-mannose + Salicin + Lactobacillus acidophilus	Initial 5-days regimen of oral 1000 mg D-mannose+ 200 mg salicin 3 times a day, followed by bid 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 (68 women, 17 men); neurogenic and non-neurogenic patients	frequency p<0.001 incontinence episodes p>0.001 (neurogenic patients)	none reported	Del Popolo et al. [27]
Multicenter randomized double-blind study	Manosar, d mannose 2 g +PAC 140 mg+ vit. C-E-A *vs.* proantocyanidin 240 mg	Once daily (prolonged release)	24 weeks	150 women	UTI recurrences p<0.05 *vs.* PAC	Diarrhea (9,52%), cefalea	Salinas-Casado et al. [13]
Clinical Trial	**Agents used**	**Dose/ n. of administrations**	**Duration**	**N. of patients**	**efficacy on rUTIs**	**Side effects**	**Reference**
double blind, prospective randomized three-arm parallel group trial	berberine, arbutin, birch+ d-mannose 420 mg (A) *vs.* berberine, arbutin, birch, forskolin+ d-man- nose 420 mg (B) *vs.* proanthocyanidins+ d-mannose 500 mg (C).	D-mannose once daily	12 weeks	72 women	<RUTI in group A and B *vs.* C (statistical significance not reported)	none reported	Genovese et al. [22]
observational retrospective clinical study	N-acetylcysteine 100 mg, D-mannose 500 mg+ Morinda citrifolia fruit extract 200 mg+ antibiotic (group A) *vs.* antibiotic alone. (group B)	1 vial every 12 h for 60 days and then 1 vial every 24 h for 4 months. Antibiotic: fosfomycin 3 grams per day for two days, to be repeated every 15 days for a total of three cycles, nitrofurantoin 1 cprs 100 mg three times a day for 6 days and ciprofloxacin 1,000 RM or prulifloxacin 600 mg 1 cps/day for 6 days.	6 months	60 women	<RUTI in group A (statistical significance not reported)	none reported	Marchiori et al. [26]

open-label feasibility study	D-mannose powder	1.5g twice daily	16 weeks	22 women group 1: multiple sclerosis (MS), no intermittent catheterization (I.C.) group 2: MS, no I.C.	< number of monthly UTIs p<0.01 (group 1), p<0.6 (group 2)	none reported	Phè et al. [21]
open study	D mannose, *H. sabdariffa*, *Lactobacillus plantarum* Lp 115	D mannose 1000 mg, *H. sabdariffa* 200 mg, *Lactobacillus plantarum* 1 mld UFC	2 weeks	100 female patients	In 87% negative urine cultures	none reported	Milandri et al. [29]
randomized parallel group intervention trial	Fosfomycin 1 sachet UROFOS® then: group A UROIAL containing S&R PACs (250 mg) with type-A proanthocyanidins (72 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. [30]

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 completely reliable. Del Popolo [28] 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 (1×10^9 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 neurogenic 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, and 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 a history of RUTI was performed [29], 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 2 g 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 urodynamic invasive procedure a phytotherapeutic product composed of D-mannose (1000 mg), H. sabdariffa (200 mg), and Lactobacillus plantarum Lp-115 (1 mld 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 [31] performed a prospective comparative study, 40 women with UTI received a single sachet of Fosfomycin Tromethamine (3 gr). 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, UROIAL™ 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.

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, cephalexin 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 [7,8]. 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 supraubic) catheter were recruited. Results are not available yet [32].

In another trial women with history of RUTI were followed over

the course of 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 feces, can colonize the peri-urethral area or vagina and then colonize the urethra to the urinary tract, where they cause UTI. A number of emerging therapies including D-mannose, probiotics and vaccination have become available for RUTI. The study carried out by Salinas-Casado evaluating a single daily formulation of 2 g D-mannose prolonged release, Manosar, represents an innovation. In fact, most commercial products with D-mannose should be taken repeatedly in the day, since the mechanism of action requires the frequent or constant presence of mannose in the urine to maintain its effectiveness for a long time.

Significant adverse events were not reported in all studies examined.

Conclusion

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 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 in-homogeneous features (neurologic and non-neurologic).

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