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Yeast Mannan Oligosaccharide Dietary Supplement In the Treatment of Chronically Acute Urinary Tract Infections: A Case Series

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ABSTRACT

Urinary tract infections (UTIs) are the most common bacterial infection experienced by women. Approximately 50 to 60% of all women in the United States will be diagnosed with UTIs at least once in their lifetime. Many of them develop recurrent infections; the frequency tends to increase with age. UTIs can be treated with antimicrobial drugs, although not without complications. The treatment of community-acquired UTI is becoming more complicated because of the increased incidence of multi-drug-resistant *Escherichia coli*, the most common cause of UTI. In this case series, we provided SUPERMANNAN (250 mg of dried, dead autolyzed yeast per capsule) to 9 women with acute and chronic UTI episodes. All patients were previously diagnosed with multiple episodes of culture-positive urinary tract infections (UTIs), placed on empirical immediate antibiotic status, and given open prescription orders by their urologists. Therapy consisted of an initial dose of 2 capsules, and then 2 additional capsules every 20 minutes for the next 2 hours, and then 2 capsules every 12 hours for the next 24 hours (total of 18 capsules in 24 hours). All women experienced UTI symptom relief within an hour and a lower frequency of recurrence after therapy. Six subjects had no adverse effects, and 3 had minimal side effects (mild, self-limiting urinary urgency without acute UTI attacks). These preliminary results suggest the oral ingestion of mannan oligosaccharides for preventing or ameliorating bacterial UTIs is feasible, and it may provide symptom relief from acute UTIs while reducing the frequency of subsequent episodes. These hypotheses should be tested in follow-up, randomized trials.

BACKGROUND

Urinary tract infections (UTIs) are the most common bacterial infection experienced by women, both pre-menopausal and menopausal [16]. Approximately 50 to 60% of all women in the United States will be diagnosed with UTIs at least once in their lifetime [18,6]. Many of them develop recurrent infections [1], and the frequency tends to be higher as women age. UTIs can be treated with antimicrobial drugs, although not without complications [10]. Treatment of community-acquired UTI is becoming more complicated because of the increased incidence of multi-drug-resistant *Escherichia coli*, which is the most common cause of UTI [12].

Typically, therapy for healthy women with uncomplicated UTIs includes antimicrobial agents (trimethoprim-sulfamethoxazole), a quinolone, or nitrofurantoin. There are many limitations to this approach, such as adverse effects from drugs and the development of drug-resistance [15]. This approach is costly, and the total cost of evaluation and treatment for all cases of UTI in 2000 was 3.5 billion (USD) [14].

The increased prevalence of drug-resistant UTIs complicates the management of these infections. With studies showing strong evidence that the acquisition of these antibiotic-resistant strains have food and animal origins, we expect the prevalence of

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antibiotic-resistant strains causing UTIs to continue to increase [12]. Of greater concern is that drug-resistant uropathogenic *E. coli* associated with uncomplicated infections such as cystitis are also becoming responsible for more severe infections, such as pyelonephritis and bacteremia in hospitalized patients [12]. Since UTIs are commonly experienced by women and usually treated with antibiotics, this problem is not likely to be controlled at the population level as long as antibiotics continue to be used. Alternative and safer means for treating UTIs exist.

Cranberry

The development of non-antibiotic-based UTI treatment to date has largely focused on products designed to decrease urine pH, such as cranberry extracts [16]. However, a recent, large, randomized controlled trial of cranberry vs placebo in 319 women with UTIs failed to find any difference in the incidence of UTIs over a 6-month period [3].

Probiotics

UTIs are also being treated with probiotics such as *lactobacillus*, purportedly related to its effects in stimulating the production of interleukin-10 (IL-10) and other immune-modulating factors [9,2]. However, the evidence for efficacy of the various probiotics against the bacteria causing UTIs is limited and contradictory, and it is hampered by trials using different strains and dosing schedules [13]; systematic reviews have failed to yield firm conclusions supporting the clinical use of probiotics for the prevention or treatment of UTIs [4]. Only a few limited strains of probiotics have demonstrated antagonism against urinary pathogens [7], and only vaginally implanted *lactobacillus* has been shown in randomized trials to reliably reduce the frequency of recurrent UTIs [17].

Mannans Versus Mannose and Synthetic Mannosides

The natural remedy proposed here to treat *E. coli* UTI is the SUPERMANNAN brand of dried, dead autolyzed yeast, which contains yeast mannan oligosaccharides (MOS). MOS produced from *Saccharomyces cerevisiae* (Alltech and Nutriteck) and from *candida guilliermondii* (Archer Daniels Midland) have been used since 1991 as an animal feed additive. SUPERMANNAN is not a probiotic.

Attempts have been made to block the attachment of uropathogenic bacteria to bladder cells with soluble mannose compounds (synthetic mannosides) [5]. However, this in vitro binding inhibition has not led to a successful UTI therapy for humans. The administration of D-mannose has also been claimed to successfully treat UTI episodes [18]. Various mannosides have been tested for binding to *E. coli* over the years, and the observations are similar—binding in vitro, sometimes with a much higher affinity than the naturally occurring hexose sugar mannose, but no lasting palliative effect on acute UTI has been demonstrated.

Biochemist Richard Katz discovered in 2005 that yeast mannan oligosaccharides (MOS) is a natural intervention for UTIs in humans, and he was granted US Patent 8 063 026 on this discovery in 2011. Yeast mannan oligosaccharides have an exceedingly complex and varied structure, arising from the varied structure of the polysaccharides in the mannan of yeast cell walls. Yeast mannan—the source of MOS in the treatment used in this paper—bears a remarkable similarity in biosynthetic origin and in chemical structure to the high mannose glycosylation universally present in eukaryotic cells, including the urinary tract epithelial cells to which *E. coli* can attach, colonize, and infect. Yeast mannan, however, bears a remarkable difference from the high mannose glycosylation of ordinary glycoproteins in its relative size and complexity; chains and side chains of mannose in yeast mannan are 1 and even 2 orders of magnitude longer; i.e., 100 or even 1 000 mannose units in length [8]. *E. coli* infecting the bladder likely metabolizes these complex mannosides, which are yeast mannan oligosaccharides or MOS. The presence of this yeast cell-wall material likely serves to opsonize the bacteria by attracting mannan-binding lectin (MBL), a normal serum protein considered a part of the lectin pathway of the innate immune system, leading to opsonophagocytosis of the bacteria.

METHODS AND MATERIALS

Subjects

Subjects were family members and friends of the principal investigators who suffered from both acute and chronic UTI episodes and requested access to MOS. We reviewed records of the principal investigators to obtain data for this report. All women provided consent to have their data used (anonymously) in this report.

All of the patients in our study had been previously diagnosed with multiple episodes of culture-positive UTIs. Thus, they had been placed on empirical, immediate antibiotic status and given open prescription orders by their urologists. They were women who wished to pursue alternate strategies of symptom management; repeated antibiotic therapy, whether following positive urine cultures or immediacy based on symptoms, was no longer desirable.

This strategy for the management of community-based chronic UTIs was supported by a randomized controlled trial (n = 309) in which women aged 18 to 70 were randomized to 5 treatment strategies: (1) empirical immediate antibiotics, (2) targeted antibiotics based on symptom score, (3) antibiotics based on dipstick tests, or (4) antibiotics after a positive urine analysis test. In this high-quality study, women randomized to immediate

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Table 1. Summary of subjects taking SUPERMANN for acute UTI.

Subject ID	Age	How long ago I started SUPERMANN	How long since my last major UTI	Since beginning SUPERMANN, the number of UTIs I've had	Since starting SUPERMANN, the number of episodes using antibiotics
1	60s	6 years, 1 month	5 years, 1 month	1	0
2	20s	5 years, 1 month	4 years	2	0
3	50s	1 year, 7 months	3 months	2	1
4	50s	1 year, 11 months	6 months	1	0
5	20s	1 year, 4 months	3 months	2	1
6	40s	3 years	3 years	1	0
7	50s	4 years	4 years	1	0
8	60s	4 months	4 months	1	0
9	50s	1 month	1 month	1	1

Data as of February 2012. In most cases, UTI was confirmed as *E. coli*-related. In the 3 recurrent cases when mild UTI symptoms were not confirmed with laboratory tests, and the patient was self-medicated with antibiotics and reported relief, this was listed as a UTI episode.

antibiotics based on symptoms, and without urinalysis, had a 37% shorter symptom duration. Furthermore, the authors concluded that there was no evidence for routine midstream urine analysis in the case management of these women [11].

Mannan Oligosaccharide Dosing Schedule

Subjects were provided with SUPERMANNAN (at least 250 mg of dried, dead autolyzed yeast per capsule; dried yeast is around 40% cell-wall material). Dosing instructions for women experiencing acute infection were: An initial dose of 2 capsules with a glass of water, followed by 2 additional capsules every 20 minutes for the next 2 hours (a total of 14 capsules in 2 hours), and then 2 capsules every 12 hours for the next 24 hours (a total of 18 capsules in 24 hours). Subjects were asked to contact their physicians if UTI symptoms did not improve within 5 hours after beginning treatment, or if they decided to switch to antibiotic therapy. Subjects were permitted to repeat another dosing course of 14 capsules over a 2-hour period if they had initial relief but symptoms returned over the following 4 days. We also asked women to keep a written diary documenting the time of occurrence, intensity, the duration of symptoms, and the doses of MOS taken.

Safety Testing

We used the MEM Elution assay (Pacific BioLabs; Hercules, CA) to test each raw material separately, and in combination, to support the safety of their use for human consumption. The MEM Elution assay uses Eagle's Minimum Elution as the extracting media and extraction conditions to test materials according to actual use conditions. Extracts can be titrated to yield a semi-quantitative measurement of cytotoxicity. After preparation, the extracts are transferred onto a layer of cells and incubated. Following incubation, the cells are examined microscopically for malformation, degeneration, and lysis.

We looked at the range of laboratory testing methods available and picked cytotoxicity testing with cultured mouse L929 cells—the "MEM Elution Assay"—as being perfectly suited to toxicity testing. This test is highly sensitive for toxicity because it applies test materials to animal tissue culture cells outside of the context of the animal's immune system (MEM Elution Assay (ISO 10993-5: 1999(E)). We felt it appropriate to apply this stringent level of safety testing. We tested each sample over a 100-fold concentration gradient.

RESULTS

Dosing Compliance and Side Effects

We initially acquired observations from 1 male and 1 female who volunteered to take 1-gram quantities of MOS. The male volunteer (aged late 50s) took approximately 1 gm of MOS daily for 2 months, with no side effects. The female volunteer (aged mid 60s) took approximately 4.5 gm of MOS over a 6-hour period on 1 occasion, and took approximately 4.5 gm of MOS over a 6-hour period on another occasion, with no side effects. In addition, 1 dog (age 5 years; 85 pounds) ate 0.4 grams of MOS daily for 2 weeks with no adverse side effects (his

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digestion improved).

Symptom Response

We next evaluated observations made from 9 females (aged mid 20s to early 60s; 7 white, 1 African American, and 1 South American) who have taken SUPERMANNAN (including Alltech BioMOS and ADM CitriStim) during an acute UTI (Table 1). These 9 women have a history of recurrent UTI that was confirmed and treated previously with antibiotics by their physicians.

The women kept a diary of symptoms and the number of capsules ingested. All women suffered dysuria, frequent urination, and hematuria. After taking approximately 0.8 grams of MOS (0.20 grams every 20 minutes) during the first hour, all 7 women experienced marked amelioration of symptoms. They took approximately 0.6 gram of MOS (0.20 grams every 20 minutes) during the second hour and UTI symptoms abated; the women could resume normal activities. The women reported that they felt no side effects.

After taking SUPERMANNAN for an acute UTI attack and several times when mild UTI symptoms recurred, 1 woman has not had a UTI for 6 years. Another woman was having infrequent UTI episodes after taking MOS the first time for an acute attack, and she was tested for UTI during pregnancy and tested negative. She had no urinary tract discomfort while pregnant. One woman took BioMOS and CitriStim under the supervision of her physician, who sent to the lab a clean sample for a urine culture before the patient took the MOS (blood and white blood cells in urine) and a urine culture 24 hours after patient took MOS. The culture tested negative for any pathogen.

Adverse Effects

Three women experienced some mild urgency without acute UTI attacks in the months after treating UTI with SUPERMANNAN. Their urine tested negative for nitrites, and their urgency was relieved with water plus either a NSAID or Azo-Standard (phenazopyridine).

DISCUSSION

These preliminary results suggest that the oral ingestion of mannan oligosaccharides for preventing or ameliorating bacterial UTIs is feasible. The ingestion of mannan oligosaccharides allowed these women, of varying age and backgrounds, to achieve symptom relief from acute UTIs without adverse side affects. Additionally, these women experienced a dramatic drop in the number of subsequent acute UTI episodes.

Three subjects reported mild UTI-like symptoms after the acute UTI episode had passed, and we do not know at this time whether mild symptoms in the weeks or months following the acute attack were related to *E. coli* or were irritations without *E. coli* present. In some instances after an acute UTI episode, a subject's urine would test negative for bacteria, and still the woman had some irritations in the urinary tract or the lower abdomen. Two of the women have used MOS for the relief of these mild symptoms, 2 other women did not get adequate relief from MOS for these mild symptoms, and they abstained from alcohol and caffeine or self-medicated with anti-inflammatory drugs or antibiotics.

Overall, these data suggest SUPERMANNAN may provide an alternative to antimicrobial therapy of acute UTI, and that SUPERMANNAN may be a novel palliative for the treatment and/or prevention of acute UTI. These hypotheses should be tested in follow-up, randomized trials.

DISCLOSURES

Clair Brown, Richard Katz, and Michael McCulloch disclose a financial interest in SUPERMANNAN.

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