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Non-antibiotic Approaches to Preventing Pediatric UTIs: a Role for D-Mannose, Cranberry, and Probiotics?

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Abstract

Purpose of Review While antibiotics have been a staple in the management and even prevention of urinary tract infections (UTIs), it is not without significant consequences due to intolerance and development of antibiotic resistant bacteria. These concerns necessitate alternatives to antibiotic use in the management of pediatric UTIs. This review seeks to evaluate non-antibiotic means of preventing UTI in the pediatric population.

Recent Findings The search for preventative alternatives to antibiotics has included D-mannose, cranberry, and probiotics. These products similarly work through competitive inhibition of uropathogens in the urinary tract.

Summary Pediatric studies exist highlighting the use of cranberry extract/juice and probiotics in UTI prevention, although significant heterogeneity amongst studies have limited overarching recommendations for their use. Data of D-mannose use is extrapolated from adult literature. More studies are required in the utility of each treatment, with some emphasis on larger sample sizes and clarifications regarding dosing and formulation.

Keywords Urinary tract infection · Pediatric · Probiotics · D-mannose · Cranberry · Proanthocyanidin

Introduction

The burden of urinary tract infections (UTIs) on patient and family and health care systems is extraordinary. UTIs are one of the most common outpatient bacterial infections, with approximately 150 million cases diagnosed worldwide each year [1, 2]. In the United States (U.S.) alone, they are responsible for 8 million physician visits per year and annual hospitalization costs of $2.8 billion dollars [3, 4].

UTIs affect 2.4–3.4% of children in the U.S. annually [5, 6]. Of these, 12–30% will have a subsequent UTI [7–10]. The long-term sequelae of UTIs is of particular concern in the pediatric population. UTIs can lead to renal scarring with resulting hypertension and renal damage that may progress to ESRD [11–13]. The risk of renal scarring only increases with the number of UTIs [14], necessitating a focus on UTI prevention in this particular population.

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Current Landscape of UTI Management

While the acute management of UTIs has centered on antibiotic use, means of preventing UTIs in UTI-prone individuals is somewhat more difficult to clarify. Surgical interventions can be used to address certain anatomic factors believed to be predisposing the pediatric population to infection, such as vesicoureteral reflux (VUR) or obstructive pathology. Antibiotics have also been utilized as a preventative measure in cases of recurrent UTIs, showing a decrease in female recurrent UTIs in the adult literature [15]. Controversy exists, however, over the efficacy of prophylactic antibiotic use to prevent UTI in the pediatric population, drawing into question its regular practice. Certain seminal pediatric studies have demonstrated that antibiotic prophylaxis decreases the risk of UTI in children with a history of prior UTI (with and without VUR) [16, 17]. Antibiotic prophylaxis to prevent UTIs is actually a recommendation in the American Urological Association guidelines in certain children with VUR [18]. A 2019 Cochrane Database systematic review looking at the impact of antibiotic prophylaxis in pediatric patients with primary VUR, however, did not show a benefit of low dose antibiotic prophylaxis in preventing repeat symptomatic and febrile UTIs [19].

In addition to questions of antibiotic prophylaxis efficacy, there are real concerns regarding antibiotic overuse and rising bacterial antibiotic resistance rates [20]. The Center for Disease Control defines antibiotic resistance as "one of the greatest public health challenges of our time" [21] and links rising patterns of resistance to antibiotic use. Concerns with use of antibiotics in UTI management exist, with a systematic review in *JAMA Pediatrics* finding an increased risk of multidrug resistant UTIs in children with VUR on antibiotics prophylaxis versus placebo [22].

Altogether, such complexities limit the use of antibiotics in UTI prevention. Antibiotic-independent means of UTI prevention are needed to provide safer and potentially more effective alternatives to limit UTI development. Such practices have included probiotic use as a means of competitive inhibition to prevent uropathogen survival and access to the urinary tract; and D-mannose and cranberry products to prevent bacterial attachment. This review will highlight the literature that exists on the use of these products in preventing pediatric UTIs.

Targeting Bacterial Means of Uropathogenesis

Means of preventing UTIs include preventing or limiting microbial access to and growth in the urinary tract. Uropathogenic bacteria arise mainly from the gastrointestinal system [23, 24]. An important first step in UTI development is the ascent of such bacteria from the perineum into the urinary tract [25]. Subsequently, the bacteria must adhere to the uroepithelium lining the urinary tract to prevent immediate loss in the urine and thus enable bacterial proliferation, biofilm formation, and bacterial infestation of the urinary tract [26–29]. These two initial steps are crucial to UTI pathogenesis. As such, preventing either of these steps from occurring could alter UTI susceptibility.

Bacteria adhere to glycoprotein receptors on uroepithelial cells via structures called pili. The type 1 pilus is one of the most characterized and highly conserved pili in the chaperone-usher pathway. It is expressed by 80–90% of uropathogenic *Escherichia coli* (UPEC) strains. It is considered "mannose-sensitive" given its ability to interact with mannosylated receptors on uroepithelial cells via FimH, a bacterial adhesin at its tip, that is inhibited by the presence of fructose [30]. The P pilus is another pili involved in bacterial attachment but is considered "mannose-resistant" due to its resistance to fructose [31]. The P pilus is overrepresented in clinical bacteria isolated from the kidney in patients with pyelonephritis while type 1 pili are linked to bladder infections [32, 33]. D-mannose and cranberry products have been investigated as potential interventions in UTI development due to their ability to limit bacterial attachment.

D-mannose

D-mannose is a monosaccharaide isomer of glucose that is normally involved in human metabolism [34, 35]. D-mannose has a similar structure to the binding site of uroepithelial glycoprotein receptors. It can thus competitively inhibit uropathogen bacterial attachment to the urinary tract [34, 36]. Formulated as a powder, it is rapidly absorbed in the gastrointestinal tract and excreted in the urine [35, 36]. In vivo studies have shown D-mannose to reduce bacteriuria in animal models of UTI [37, 38].

Overall, there are relatively few clinical studies of D-mannose use in UTI prophylaxis, with no studies performed in children. Thus, we can only extrapolate the potential utility of D-mannose in preventing UTIs from adult data. In one of the only randomized controlled trials of D-mannose monotherapy use in UTI prophylaxis, women with recurrent UTIs were randomly assigning to (1) daily D-mannose (2 g) ($n=103$); (2) daily antibiotic (nitrofurantoin 50 mg) ($n=103$); or (3) no intervention ($n=102$) [34]. Daily D-mannose or antibiotics significantly reduced the rate of recurrent UTI compared to no intervention after 6 months of use (14.6% and 20.4% vs. 60.8%, respectively; $p<0.001$). There was no significant difference in UTI recurrence between those on D-mannose and nitrofurantoin; D-mannose use, however, had fewer patient reported side effects than nitrofurantoin (7.8 vs. 27.2%; $p<0.0001$). This single study would suggest that D-mannose is as effective as antibiotics in preventing adult UTIs, with a benefit of fewer side effects. Further studies are needed, with a randomized controlled double-blinded study proposed in the UK (the MERIT study) to start in 2021, comparing D-mannose to placebo alone in preventing recurrent UTIs [39].

Other adult studies have evaluated D-mannose as part of a panel of ingredients taken for UTI prophylaxis. Typically, these studies have found that D-mannose added to varying cocktails of dietary supplements decreases UTIs compared to no treatment when taken by adult women (both premenopausal and peri-menopausal) [40–42]. The studies, however, have generally been small with inconsistent supplemental products combined with D-mannose.

Systematic reviews of D-mannose use in adult UTI prevention have typically found some benefit, though acknowledging concerns regarding the small overall number of studies and issues with study quality, marred by varied study design and poor description of dosing, frequency, and duration of use. In addition, none of these reviews included children [43, 44•, 45]. Lenger et al. found a pooled relative risk of UTI recurrence when comparing D-mannose to placebo of 0.23 (95% CI 0.14–0.37), showing a protective effect of D-mannose compared to placebo. The pooled relative risk of UTI recurrence when comparing D-mannose to antibiotic prophylaxis was 0.39 (95% CI 0.12–1.25), suggesting a possible similar effectiveness between the

two therapies. They concluded that D-mannose appeared protective of recurrent UTIs when compared to placebo and is possibly as effective as antibiotics [44•]. Compliance was high, with diarrhea reported as the primary side effect in 8% of patients taking 2 g of D-mannose for at least 6 months [43].

Unfortunately, concerns regarding the bioavailability of D-mannose may limit its use [30, 35, 36]. Synthetic carbohydrate-based drugs, called glycomimetics, are being investigated as more potent inhibitors of FimH binding [30, 37]. Trying to improve upon bacterial attachment blockade with either increased affinity for uroepithelial glycoreceptors or through direct FimH antagonism, and as either as monotherapy or in combination with other compounds like antibiotics, is of great interest and a future direction of development [35]. In addition, future studies clearly need to include pediatric populations.

Cranberry

Cranberry has also been found to affect bacterial attachment in the urinary tract [46, 47]. While initially thought to limit bacterial viability through urine acidification [48, 49], it is now known that cranberry products actually work through a variety of other means, including direct impedance of FimH or P pilus mediated bacterial binding or through increased Tamm-Horsfall expression which itself limits bacterial adherence to the uroepithelium, as well as by altering bacterial virulence factors such as flagella and P pilus expression [30, 46, 47, 50–52]. There are likely multiple components within cranberries responsible for its antibacterial/antiadhesive properties, but those identified thus far include proanthocyanidin (PAC) and B-ring substituted flavones and flavonols [30, 47].

While in vitro studies have demonstrated a role for cranberry products in preventing bacterial attachment [51, 53], clinical data has been more conflicting in demonstrating its usefulness in UTI prevention. Results in adult literature have been varied. An older study demonstrated that cranberry juice reduced bacteriuria and pyuria in elderly women by nearly in half [48]. A more recent randomized controlled trial comparing cranberry juice to placebo did not find an overall significant reduction in UTI in postmenopausal women ($p=0.82$) [54].

The efficacy of cranberry products in preventing pediatric UTIs is even less clear. In a double-blinded randomized controlled study on the impact of cranberry juice vs. placebo on overall bacterial colonization of children, cranberry juice was not found to significantly affect bacterial colonization in the respiratory tract or colon. In addition, there were no significant differences in common infectious diseases noted between groups over 3 months of treatment. There was some question if the dose of cranberry juice was too low to be effective and the study was not specifically designed to compare the incidence of UTI between groups [55].

There are few randomized trials specifically evaluating the impact of cranberry ingestion in preventing UTI in children, making it difficult to draw conclusions about its benefit. Studies have been performed in relatively healthy populations as well as those with anatomic/neurologic anomalies. Individual studies are highlighted in Table 1. In the largest study comparing the impact of cranberry juice vs. placebo on developing a pediatric UTI, the outcome was mixed. The authors randomized healthy, predominantly female patients with a history of at least 1 UTI to either cranberry juice or placebo. The number of children experiencing an UTI was not different between groups ($p=0.21$); there was, however, a significant reduction in the density of UTIs in the cranberry juice group ($p=0.035$). Antibiotic use was thus also reduced in those taking cranberry juice [56]. Two other randomized controlled studies found an overall positive effect of cranberry juice and/or its products on recurrent UTIs as compared to either placebo alone or also including *Lactobacillus* [31, 50]. Notably, there was a high dropout rate in one of the studies (30%), with 3 patients refusing to drink the juice presumably due to the taste [50].

Pediatric studies comparing cranberry juice to antibiotic prophylaxis are particularly lacking. In the only study comparing cranberry juice to antibiotics taken daily in children with VUR, investigators found that cranberry juice had a comparable impact on UTI occurrence as the antibiotic cefaclor. Study size was noticeably small, however, with only 12 children in the cranberry group vs. 19 taking cefaclor. Overall, cranberry juice tolerability seemed high, with only one patient unable to drink it due to tartness [57].

There have been several studies evaluating cranberry juice intake and UTIs in children with neurogenic bladder (NGB) on clean intermittent catheterization (CIC), with mixed results. In an early, single-blinded crossover randomized control trial, there was no significant difference in UTIs between those taking cranberry juice vs. water ($p=0.6$). There was a high dropout rate due to issues drinking the cranberry juice, with only about half of patients completing the study [58]. A subsequent double-blinded placebo controlled crossover trial did not find a difference between those on cranberry concentrate or placebo regarding rates of bacteriuria on regular urine sample collection or symptomatic UTI. It was not, however, powered to evaluate for differences in rates of UTI [59]. In the most recent randomized controlled study comparing cranberry capsule use to placebo over 6 month increments, investigators found a significantly lower rate of UTIs ($p=0.012$) and pyuria ($p<0.0001$) when individuals were taking the cranberry capsules. There were no adverse events/side effects recorded in this study, with no dropouts [60].

Table 1 Pediatric studies evaluating use of cranberry products in UTI prevention

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Studies in otherwise healthy children—can have vesicoureteral reflux (VUR)									
Salo et al. (2012)	Double-blind randomized placebo-controlled trial	Healthy children; low grade (1/2) VUR only; history of at least 1 UTI	255	1) Cranberry juice ($n=126$; 115 female) 2) Placebo ($n=129$; 117 female)	1) Commercially available cranberry juice containing 41 g cranberry concentrate in 1L of juice 2) Placebo drink without either fruit or berry extracts	1) Cranberry juice group: mean age 3.8 years (SD 2.5) 2) Placebo group: mean age 4.5 years (SD 2.9)	6 months	1 year	Incidence UTI: -Cranberry juice vs. placebo: 16 vs. 22%; $p=0.21$ UTI incidence density per year: -Cranberry juice vs. placebo: 0.25 vs. 0.41; $p=0.035$ Need for antibiotic use was 6 days less per year in cranberry juice group ($p<0.001$) 27 children dropped out: -Cranberry juice group: 16 -Placebo group: 11
Afshar et al. (2012)	Randomized placebo-controlled trial	Healthy children without anatomic abnormalities (could have primary VUR but did not specify grade); history of at least 2 nonfebrile UTIs	40	1) Cranberry juice with proanthocyanidin (PAC) ($n=20$; female 19) 2) Cranberry juice without proanthocyanidin (PAC) ($n=20$; female 20)	1) Cranberry juice with 37% PAC at 2 cc/kg 2) Cranberry juice with no PAC of same volume	Mean age: 9.5 years Median age: 7 years 1) PAC group: median age 7 years 2) No PAC group: median age 7 years	1 year	1 year	Average incidence UTI per patient per year: -PAC group vs. no PAC group: 0.4 vs. 1.15; $p=0.045$ -65% reduction in risk UTI 12 children dropped out -PAC: 6 -No PAC: 6 -3 dropped out due to refusal to drink -4 dropped out due to family perception the juice was ineffective

Table 1 (continued)

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Ferrara et al. (2009)	Randomized controlled trial	Healthy children without structural obstructions or urinary tract deformity; history of more than 1 *E. coli* UTI	84	1) Cranberry juice ($n=28$) 2) *Lactobacillus* GG ($n=27$) 3) Controls ($n=29$) (84 girls)	1) Cranberry concentrate juice 50 ml/daily (7.5 g of cranberry concentrate and 1.7 g of lingonberry concentrate) *2) Lactobacillus* GG drink (4×10^7/100 ml) 5 days/month for 6 months	Mean age: 7.5 years	6 months	6 months	Incidence UTI: -Cranberry juice (18.5%) vs. *Lactobacillus* (42.3%) vs. Controls (48.1%); $p<0.05$ No negative reactions were observed except a "few reports about the taste of the cranberry juice" 4 subjects withdrew (1 from cranberry juice; 1 from *Lactobacillus*; 2 from controls)
Nishizaki et al. (2009)	Observational cohort study	Children with VUR (except grade 5)	31	1) Cranberry juice ($n=12$; 5 female) 2) Antibiotic prophylaxis ($n=19$; 8 female)	1) Cranberry juice 50% concentrated per day (100 ml) 2) Cefaclor antibiotic 5–10 mg/kg daily	1) Cranberry juice group: mean age 32.5 months (± 19.6) 2) Cefaclor group: mean age 18.2 months (± 22.9)	1) Cranberry juice group: mean 17.2 months (range 3–27) 2) Cefaclor group: mean 10.2 months (range 5–15)	1) Cranberry juice group: 206-month study period 2) Cefaclor group: 194-month study period	Number UTIs: -Cranberry juice vs. antibiotic: 2 vs. 2; $p>0.05$ 1 patient unable to drink Cranberry juice due to "its tartness" 1 patient in cefaclor group had loose stool
Studies in patients with neurogenic bladder (NGB) on clean intermittent catheterization (CIC)									
Foda et al. (1995)	Randomized single-blind crossover study	Children with NGB on CIC		1) Cranberry juice 2) Water	1) Cranberry juice 30% concentrate (15 ml/kg per day) 2) Water Cranberry juice × 6 months followed by water × 6 months or vice versa		12 months	12 months	No significant difference in UTI between interventions ($p=0.6$) 19 children dropped out -12 dropped out due to drinking the Cranberry juice

Table 1 (continued)

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Schlager et al. (1999)	Double-blind, placebo-controlled, crossover study	Children with NGB on CIC	15	1) Cranberry concentrate 2) Placebo (8 females)	1) Cranberry concentrate (30% concentrate at 300 ml/day) 2) Placebo concentrate Cranberry concentrate ×3 months followed by placebo × 3 months or vice versa	5 children were 2–5 years old 10 children were 6–18 years old	6 months	6 months	In both Cranberry concentrate and placebo: 75% of samples collected on weekly basis had pathogens Number UTIs: -Cranberry concentrate vs. placebo: 3 vs. 3; $p > 0.05$
Mutlu and Ekinci (2012)	Single-blind randomized controlled, crossover study	Children with NGB on CIC	20	1) Cranberry capsule 2) Placebo (13 females)	1) Cranberry extract tablet 2) Placebo capsule Placebo capsule ×6 months followed by Cranberry tablet ×6 months or vice versa	Mean age: 7.25 ± 3.49 (4, 18) years	12 months	120 patient months	UTI rate per year -Cranberry vs. placebo: 0.5 vs. 0.7; $p = 0.012$ Rate pyuria -Cranberry vs. placebo: 10 vs. 80%; $p < 0.0001$

Due to the overall small number of pediatric studies, most systematic reviews on cranberry juice use in UTI prevention combine the results of studies in adults and children, with conflicting results. The most recent Cochrane Database systematic review did not recommend using cranberry juice to prevent UTIs. This review of 24 studies totaling 4473 patients did not find that cranberry products when compared to placebo significantly reduced overall symptomatic UTI (RR 0.86, 95% CI 0.71–1.04) or UTIs in specific populations, including women (RR 0.74, 95% CI 0.42–1.31) or children (RR 0.48, 95% CI 0.19–1.22). They did find that the cranberry juice was not significantly different in efficacy compared to antibiotics for women (RR 1.31, 95% CI 0.85–2.02) and children (RR 0.69, 95% CI 0.32–1.51). They noted issues with compliance, reporting high dropout rates attributed to issues with cranberry juice palatability. The authors also noted issues with quantification and standardization of cranberry product dosing [61]. In contrast, another systematic review of a smaller number of studies found a positive effect of cranberry products in protecting against UTIs. They found cranberry prevented UTIs in women (RR 0.49, 95% CI 0.34–0.73) and children (RR 0.33, 95% CI 0.16–0.69). In general, cranberry use in studies was at least 6 months. Interestingly, they found that cranberry juice was more effective than cranberry capsules or tablets in a subgroup analysis, possibly related to hydration status or due to protective mechanisms of other unknown substances in the juice form. They also recommended at least twice daily dosing [62].

In the only systematic review of pediatric studies, cranberry products were found as effective as antibiotic prophylaxis (RR 0.92, 95% CI 0.56–1.5) (although based upon only a single study comparing the two treatments) and better than no therapy or placebo (RR 0.48, 95% 0.28–0.8) in preventing UTIs in children with normal urinary tracts. Interestingly, this review did not report on patient compliance. It did note a high or at least unclear risk of bias in all studies reviewed; as a result, the authors hesitated to universally recommend cranberry prophylaxis in children [63••].

As previously noted, cranberry dosing has not been standardized. In vitro studies have suggested a bioactivity threshold of 60 ug PAC/ml [51]. Clinical studies in adults suggest dosing between 36 and 72 mg of PAC containing cranberry product per day [48, 64], with up to 300 ml of 5 ml/kg cranberry juice per day suggested in children. Consideration must be given as to the acidity of cranberry juice that thus limits its tolerability [61]. Pure cranberry juice is too acidic (pH < 2) to ingest; cranberry cocktail is typically 33% cranberry juice [65]. While overall considered safe, there has been concern that cranberry juice may increase the risk of developing calcium oxalate and uric acid stones, but without conclusive data [66–68].

Competitive Inhibition Through Probiotics

There has been a growing interest in the use of probiotics to alter patient UTI susceptibility by modifying a patient's own gastrointestinal and perineal flora. In general, our bodies are comprised of a host of bacteria with beneficial health effects to prevent pathogenic bacterial infection [69, 70]. The flora of the vagina is important in maintaining good urinary tract health. *Lactobacilli* dominate the healthy flora of premenopausal women [71, 72]. They protect the urinary tract by preventing bacterial adhesion and producing antimicrobial factors such as acids, hydrogen peroxide, and bacteriocins [70]. Given the majority of uropathogens arise from the microbiota of one's own gastrointestinal tract, methods to prevent ascending spread of bacteria from this ecosystem to the urinary tract have focused on boosting the surrounding healthy microbiota via probiotics and altering the composition of the potential uropathogens present to help maintain and improve the microbial balance in the human body [69, 73].

Probiotics are live microbial organisms that confer a health benefit on the host [74]. The most common microbes used as probiotics are strains of lactic acid bacteria, a clade of gram-positive bacteria that lower environmental pH due to lactic acid formation through lactose digestion. *Lactobacillus* and *Bifidobacterium* are examples of lactic acid bacteria and have been shown in vitro to have antibacterial activity [75]. Their protective effects are believed to be multiple, including preventing bacterial binding and nutrient acquisition through competitive inhibition and the secretion of biosurfactants that impede uropathogen adherence, producing antimicrobial substances such as bacteriocins, hydrogen peroxide, antiseptics, and acidic substances like lactic acid, modulating innate immunity, and even directly impacting bacterial virulence by disrupting biofilm formation [70, 72, 73, 75–78].

There have been studies showing alterations in gut and perineal flora are associated with an increased risk of UTI [25, 79]. Initial studies in adults have demonstrated a lower rate of pathogens in the perineum of healthy patients compared to those with a history of UTI, despite similar perineal anatomy [80]. More recently, specific imbalances or depletion of *Lactobacilli* in the vagina or perineum have been associated with an increased risk of UTI [81–83]. While there are fewer reports in the pediatric literature, the studies that exist also report similar associations between perturbations in the perineal microbiome and increased risk of UTI [84]. A study specifically evaluating *Lactobacillus* bacterial counts in infants found that infants with a history of UTI had significantly lower stool, urine, and periurethral counts compared to controls ($p < 0.05$) [85].

As such, there has been much interest in using probiotics to alter UTI risk. Early in vitro work demonstrated the ability of indigenous bacteria to block the attachment of UPEC to human uroepithelial cells [86]. Further studies have demonstrated that lactic acid bacteria do have antimicrobial activity against uropathogenic bacteria [75, 78].

Clinical trials evaluating the efficacy of probiotic use in children to prevent UTIs have been promising. Studies are summarized in Table 2. In general, studies have been performed in those that are high risk for infection, such as those hospitalized or in those with certain urinary tract abnormalities that predispose to upper tract infection, like VUR. In studies evaluating probiotic use exclusively on preventing UTI, most studies only include patients with a prior history of UTI. Probiotic use has been compared to placebo, antibiotics, and even cranberry supplementation.

One of the first reports specifically looking at using probiotics in a child as a prophylactic means to prevent UTI was a case report of a 6-year-old female with recurrent UTIs who was given *Lactobacillus acidophilus* twice a day for 1 month then once daily indefinitely. The case reported its successful use in eliminating the *E. coli* serotype found in the patient's urine at time of positive culture but also continuously found in her feces and subsequent resolution of her recurrent UTIs [87].

Studies comparing probiotics to antibiotic use on recurrent UTI in patients with VUR subsequently emerged. A group out of South Korea has performed several studies evaluating the impact of probiotic (*L. acidophilus*) to trimethoprim/sulfamethoxazole prophylaxis either in children with persistent VUR after 1 year of antibiotic prophylaxis or in infants with VUR found after first febrile UTI [88••, 89]. In both randomized controlled studies, they found daily probiotic use as effective as prophylactic dosing of trimethoprim/sulfamethoxazole on preventing UTIs. They did find a significant benefit of probiotics on lowering *E. coli* antibiotic resistance rates to trimethoprim/sulfamethoxazole, and even gentamicin in one of their studies. In both studies, however, their patient recruitment did not meet their original power calculation. Another randomized controlled study compared the combination of a probiotic (*L. acidophilus* and *B. lactis*) with daily antibiotic prophylaxis (nitrofurantoin) to that of daily antibiotic prophylaxis alone in children with recurrent UTIs and unilateral VUR [90]. In 3 years of follow-up, the investigators did not find a significant difference in UTIs between groups ($p = 0.4$). Probiotics in combination with antibiotics may decrease febrile UTIs as compared to antibiotic alone, but only after prolonged usage ($p = 0.03$). They did find that those on probiotics who had an UTI had *E. coli* strains that were more sensitive to nitrofurantoin ($p = 0.02$). They concluded that probiotics may be of use in supplementing antibiotic use.

Table 2 Pediatric studies evaluating impact of probiotics on UTI occurrence

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Studies with multiple outcomes, including UTI									
Kumar et al. (2013)	Retrospective study	Children in PICU; on broad spectrum antibiotics a minimum of 48 h		1) Probiotic sachet ($n=344$; 110 females) 2) Controls ($n=376$; 106 females)	1) Probiotic sachet containing *Lactobacillus acidophilus, L. rhamnosum, Bifidobacterium longum, B. bifidum, Saccharomyces boulardii,* and *Streptococcus thermophilus* BID for 7 days	1) Probiotic group: mean age 4.2 years (SD 3.7) 2) Controls: mean age 4.1 years (SD 3.8)	"routinely gave probiotics… to all patients receiving broad-spectrum antibiotics for more than 48 h"	Mean days in PICU: 1) Probiotic group: 11.3 (SEM 0.5) 2) Controls: 12 (SEM 0.5)	Incidence of candidemia: -Probiotic vs. control: 1.2 vs. 3.7%; $p=0.03$ Incidence of candiduria: -Probiotic vs. control: 10.7 vs. 22%; $p=0.0001$ Incidence UTI: -Probiotics vs. control: 14.2 vs. 19.1%; $p=0.08$
Dani et al. (2002)	Randomized double-blind study	Infants in NICU: EGA < 33 weeks or birthweight < 1500 g	585	1) *Lactobacillus* GG ($n=295$) 2) Placebo ($n=290$)	1) Standard milk feed supplement with *Lactobacillus* GG (6×10^9 CFU/day) starting with first feed until discharge 2) Standard milk feed with placebo	1) Probiotic group: mean EGA 30.8 weeks (±2.5) 2) Placebo group: mean EGA 30.7 weeks (±2.3)	1) Probiotic: mean days 47.3 (±26.0) 2) Placebo: mean days: 48.2 (±24.3)	1) Probiotic: mean days 47.3 (±26.0) 2) Placebo: mean days: 48.2 (±24.3)	Incidence of necrotizing enterocolitis: -Probiotic vs. placebo: 1.4 vs. 2.8%; $p>0.05$ Incidence bacterial sepsis: -Probiotic vs. placebo: 4.7 vs. 4.1%; $p>0.05$ Incidence UTI: -Probiotic vs. placebo: 3.4 vs. 5.2%; $p>0.05$

Table 2 (continued)

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Kara et al. (2019)	Randomized prospective study	Malnourished children (body weight and height below -2 SD)	71	1) Probiotic supplementation ($n=38$; 26 females) 2) Controls ($n=33$ finished; 20 females)	1) Probiotic supplementation of *L. rhamnosus* GG (10^9) daily with calorie and protein-appropriate diet 2) Calorie and protein-appropriate diet	1) Probiotic group: mean age 22.32 months (±13.41) 2) Controls: mean age 28.82 months (±16.51)	3 months	3 months	Frequency upper respiratory tract infections -Probiotic vs. controls: 0.24 vs. 0.73; $p<0.001$ Frequency hospitalizations -Probiotic vs. controls: 0.03 vs. 0.18; $p<0.002$ Frequency total infections -Probiotic vs. controls: 0.32 vs. 1.21; $p<0.001$ Frequency UTIs during 2nd month -Probiotic vs. controls: 0 vs. 0.12; $p=0.02$
Maldonado et al. (2012)	Randomize controlled double-blinded study	Healthy infants exclusively formula fed		1) Probiotic supplementation ($n=97$; 43 female) 2) Controls ($n=91$; 51 females)	1) Formula supplemented with *L. fermentum* (2×10^8 CFU/day) + galactooligosaccharide (0.4 g/100 mL) 2) Formula supplemented with galactooligosaccharide (0.4 g/100 mL) alone	1) Probiotic group: mean age 6.5 months (±1.2) 2) Control group: mean age: 6.5 months (±1.3)	6 months	6 months	Incidence GI infections -Probiotic vs. controls: 0.2 vs. 0.4; $p=0.032$ Incidence respiratory infections -Probiotic vs. controls: 1.1 vs. 1.5; $p=0.022$ Incidence UTI: -Probiotic vs. controls: 0.01 vs. 0.06; $p=0.083$
Studies focused exclusively on UTI outcome									
Sadeghi-bojd et al. (2020)	Randomized controlled double-blinded trial	Children with first febrile UTI and normal RUS and without history of VUR	181	1) Probiotic ($n=91$; 52 females) 2) Placebo ($n=90$; 50 females)	1) Probiotic capsule 500 mg (*L. acidophils* 15×10^9 CFU, *L. rhamnosus* 1×10^9 CFU, *B. bifidum* 4×10^9 CFU, *B. lactis* 15×10^9 CFU) dissolved in 5% dextrose water (500 mg/10 ml) given as 0.5 ml (25 mg)/kg BID 2) Placebo (0.5 ml/kg) of drinking water BID	1) Probiotic group: mean age 3.3 years (±1.5) 2) Placebo group: mean age 3.6 years (±0.9)	18 months	18 months	Composite cure of UTI: -Probiotic vs. placebo: 96.7 vs. 83.3%; $p=0.02$ No significant difference in causative organisms between groups No adverse events

Table 2 (continued)

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Lee et al. (2016)	Retrospective review	Infants diagnosed with acute pyelonephritis with normal urinary tracts on RUS and VCUG		1) Probiotics ($n=73$; 23 female) 2) Antibiotic prophylaxis ($n=50$; 11 female) 3) Control ($n=68$; 14 female)	1) *L. acidophilus* (10^8 CFU/g BID) or *L. acidophilus* + *L. rhamnosus* (2×10^9 CFU/g BID) 2) Trimethoprim/ sulfamethoxazole 2/10 mg/ kg qhs 3) No intervention	Age months (not specified if median or mean) 1) Probiotic: 4.5 (±2.4) 2) Antibiotic: 4.6 (±2.8) 3) Control: 4.2 (±2.5)	6 months	6 months	Incidence UTI -Probiotic vs. controls: 8.2 vs. 20.6%; $p=0.035$ -Probiotic vs. antibiotic: 8.2 vs. 10%; $p=0.532$ -Antibiotic vs. controls: 10 vs. 20.6%; $p=0.415$ Incidence UTI on multivariable analysis: -Probiotic vs. controls in males only: 6 vs. 20.4%; $p=0.032$ Resistance rate of *E. coli* to trimethoprim/ sulfamethoxazole: -Antibiotic (100%) vs. Probiotic (25%) vs. Control (42%); $p=0.008$ Sample size less than calculated originally for power 80% (only powered to 78%)
Lee and Lee (2015)	Randomized controlled study	Infants with primary VUR diagnosed after first febrile UTI	128	1) Probiotics ($n=64$; 26 female) 2) Antibiotic prophylaxis ($n=64$; 20 female)	1) *L. acidophils* 10^8 CFU/g BID 2) Trimethoprim/ sulfamethoxazole 2/10 mg/kg qhs or amoxicillin 10 mg/kg day if < 2 months old	Age months (not specified if median or mean) 1) Probiotics: 4.7 (±3.6) 2) Antibiotics: 5.9 (±5.5)	1 year	1 year	Incidence UTI: -Probiotic vs. antibiotics: 33 vs. 41%; $p=0.348$ Resistance rate of *E. coli* to trimethoprim/ sulfamethoxazole: -Antibiotic vs. probiotic: 100 vs. 27%; $p<0.03$ Resistance rate of *E. coli* to gentamicin: -Antibiotic vs. probiotic: 46 vs. 9%; $p<0.02$

Table 2 (continued)

Study	Design	Patient demographic	N	Groups	Dosing	Age groups	Duration treatment	Follow-up	Outcome
Lee et al. (2007)	Randomized controlled study	Children with persistent VUR after antibiotic prophylaxis for 1 year (unclear if had original UTI)	120	1) Probiotics ($n=60$; 16 females) 2) Antibiotic prophylaxis ($n=60$; 15 females)	1) *L. acidophilus* 10^8 CFU/g BID 2) Trimethoprim/sulfamethoxazole 2/10 mg/kg qhs	Age months (not specified if median or mean) 1) Probiotics: 19 (±12.1) 2) Antibiotics: 21 (±11.4)	12 months	12 months	Incidence UTI: -Probiotic vs. antibiotics: 18.3 vs. 21.6%; $p=0.926$ Resistance rate of *E. coli* to trimethoprim/sulfamethoxazole: -Probiotic vs. antibiotic: 43 vs. 100%; $p<0.019$ Sample size less than calculated originally for power 80% (only powered to 78%)
Mohensi et al. (2013)	Randomized clinical trial	History of at least 2 UTIs and unilateral VUR	85	1) Combo group (antibiotic and probiotic) ($n=41$; 26 female) 2) Antibiotic alone ($n=44$; 30 female)	1) Probiotic (*L. acidophilus* and *B. lactis* 10^7 ml at 0.25 ml/kg TID) + nitrofurantoin 1 mg/kg daily 2) Nitrofurantoin 1 mg/kg daily alone	1) Combo group: mean age 8.3 years (±3.1) 2) Antibiotic only group: mean age 8 years (±3)	Mean time of probiotic therapy was 2 years	3 years	Overall incidence of UTI: -Combo vs. antibiotic alone: 39 vs. 50%; $p=0.4$ Incidence per person year of febrile UTIs in last year of study -Combo vs. antibiotic alone 0 vs. 0.13; $p=0.03$ Number cases of *E. coli* resistant to nitrofurantoin in the last year of study: -Probiotic vs. antibiotic: 0 vs. 6; $p=0.02$ No observed side effects
Pending study with primary outcome UTI									
Daniel et al. (2020)	Randomized placebo controlled, double-blinded, superiority trial	Children with recurrent UTIs in last year	116	1) Probiotic 2) Placebo	1) Probiotic (*L. rhmanosus* and *L. plantarum* 10^9 CFU [2 g] each daily 2) Placebo powder daily	3–18 years	90 days	12 months	Primary outcome: frequency of recurrent UTI during intervention and in 9 months after intervention Proposed completion 2021

There have been several studies evaluating the role of probiotics in healthy children with presumed normal urinary tracts. These studies have tended to include an arm of no treatment to which to compare probiotic use. Two relatively large studies, one performed in toddlers and one in infants, found probiotic use significantly lowered UTI rates compared to no prophylaxis [91, 92]. In the study performed in infants, however, probiotics only maintained their superiority to no prophylaxis in those of male gender on multivariable analysis ($p = 0.032$) [91]. In a study of completely healthy infants without apparent history of UTI, randomized to formula either supplemented with probiotics or not, they did not find a difference in incidence of UTIs after 6 months. The overall incidence of UTI was low, however, potentially underpowering their results [93]. Similarly, a previously discussed study comparing probiotic use to cranberry use or no treatment at all in healthy females found the incidence of UTI was no different between probiotic use and no intervention (42.3 vs. 48.1%) [31]. Cranberry use was actually more successful in preventing UTI than both probiotic use and no intervention ($p < 0.05$).

Systematic reviews and meta-analyses have been performed to try and formulate some conclusions regarding probiotic use in children. In general, these reviews do not recommend the use of probiotics to prevent UTIs due to study heterogeneity impeding conclusive findings [94]. A review by Hosseini et al. in 2017 did not find a benefit of probiotic use in children in reducing the incidence of UTI (RR 0.93, 95% CI 0.85–1.03) and its recurrence (RR 0.93, 95% CI 0.85–1.02). While there was no apparent benefit of probiotic monotherapy on preventing UTI (RR 0.96, 95% CI 0.89–1.04), probiotics as an adjuvant therapy to antibiotics appeared to reduce the incidence of UTI (RR 0.92, 95% CI 0.85–0.99) [95•]. Of promise are planned future studies, including a randomized controlled double-blinded study comparing *L. rhamnosus* and *L. plantarum* use versus placebo in children 3–18 years of age [96]. In addition, future studies may include use of probiotics locally within the bladder and/or its evaluation in certain special populations such as those with NGB [97].

While probiotics show some promise, their role in preventing pediatric UTIs is still unclear. Pediatric studies of probiotic use tend to be small if not underpowered with significant heterogeneity, preventing an ability to perform meta-analyses. Data is lacking identifying an optimal strain, dosage, formulation, and duration of treatment [69]. In addition, there is no governing agency overlooking quality control in the U.S. [76, 98]. While generally considered safe with only mild adverse effects reported such as abdominal discomfort or flatulence [98], there have been rare reports of *Lactobacillus* sepsis with probiotic use in pediatric patients [99–103]. Cases tended to involve those with complex medical histories, including immune compromise (including prematurity), prior surgery, prior antibiotic therapy, GI abnormalities, and existing central venous lines. In addition, the long-term effects of probiotic use in children are unclear.

Conclusions

UTI prevention has significant beneficial ramifications for patient and family, particularly in the pediatric population. While antibiotics can be used to prevent UTIs, their use is not without controversy and risk, necessitating investigation of alternative means of prevention. D-mannose has not been investigated enough in the pediatric population to be able to draw conclusions regarding its use. Cranberry could be promising but concerns regarding its tolerability may limit its use. Probiotics show promise as being more effective than no treatment while as effective as antibiotic prophylaxis alone or even potentiating the effects in combination with antibiotics. Studies of higher rigor are needed to enable more definitive conclusions. The presence of upcoming studies is encouraging and shows promise of ongoing research in these treatment modalities.

Compliance with Ethical Standards

Conflict of Interest I have no conflict of interest with this content.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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•• Of major importance

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