

Probiotics for Prophylaxis and Treatment of Urinary Tract Infections in Children

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Abstract

Context: Urinary tract infection (UTI) is a common and important problem during childhood that may cause chronic morbidities. Live beneficial microorganisms called probiotics have been investigated for their use in the prophylaxis and treatment of UTIs in children.

Evidence Acquisition: We aimed to discuss data about use, mechanisms and effects of probiotics on pediatric UTIs. We searched the literature, including PubMed, Medline and Cochrane databases from January 2001 to May 2016, and limited the search to English language. We used the key words probiotics, urinary tract infection, treatment, prophylaxis and children.

Results: Probiotics inhibit uropathogens by competition for receptors and nutrients, direct killing, immune modulation and production of inhibitory metabolites. There are many organisms that have been used as probiotics. *Lactobacillus* sp., *Bifidobacterium* sp. and *Saccharomyces boulardii* are the most commonly used and investigated probiotics. Although there are various benefits of probiotics for the pediatric population, some reports indicate rare complications such as bacteremia, sepsis, endocarditis, meningitis, UTI, abscesses, fungemia, pneumonia and chorioamnionitis. However, these are much less than the benefits of probiotics yet should be kept in mind. Continuing laboratory and clinical studies are encouraging the use of this strategy for the prevention and treatment of UTI in children.

Conclusions: Probiotics can be used as a natural and efficient alternative to antibiotics in UTI prophylaxis and treatment in children.

Keywords: Probiotics, Urinary Tract Infection, Treatment, Prophylaxis, Children

1. Context

Urinary tract infection (UTI) is a very common problem in pediatric practice, which may lead to long term health issues such as renal scar, renal failure and hypertension, especially when it is recurrent. Urinary tract infection also increases the healthcare costs of countries. There are various bacteria, viruses, fungi and parasites that cause UTI, but the most frequently seen agent is found to be *Escherichia coli* (*E. coli*) (1). Treatment of UTI with antibiotics has led to some side effects, destruction of normal flora and emerging resistant microorganisms are a worldwide difficulty. Non-antibiotic methods have come to be effective against UTI without increasing the resistance rates. Probiotics in this aspect, are beneficial live microorganisms utilized in treatment of several infectious diseases and shown to be effective in UTI prophylaxis and treatment as a current concept. Avoiding antibiotic resistance, restoring a healthy microbiota and supporting the immune system are all exhibited by probiotics (2). In this review, we aimed to discuss current data about the role, mechanisms and effects of probiotics in prophylaxis and treatment of UTIs during childhood.

2. Evidence Acquisition

We performed a literature search with PubMed, Medline and Cochrane database from January 2001 to May 2016 to select articles about the use and efficacy of probiotics in prophylaxis and treatment of UTIs in children. We limited our search to literature in the English language. We used the key words probiotics, urinary tract infection, treatment, prophylaxis and children.

3. Mechanisms Behind Action

Probiotics have many abilities such as adhesion to cells, avoiding adhesion and aggregation of pathogenic agents and influence the components of flora and activate the immune system. They play a role in the modification of mucosal immunity and enhance other procedures such as production of cytokines, secretion of IgA, phagocytosis and production of inhibitory substances. These substances, which are inhibitory to pathogenic microorganisms are hydrogen peroxide (H₂O₂), heat stable bacteriocins, antifungal peptides and pH-reducing organic acids like lactic acid and acetic acid. They all have effects

by directly killing pathogens, altering the pH and receptors. Bacteriocins are antimicrobial peptides that influence other bacteria by formation of pores and inhibition of cell wall synthesis.

Probiotics compete with pathogens for nutrition, they avoid the attachment of pathogens and activity of toxins produced by microorganisms. They increase the proliferation of mucosa, which results in better barrier defence. Probiotics also modify innate and adaptive immune systems and avoid translocation of bacterial pathogens. Another mechanism of probiotics against uropathogens is activation of NF-kappa- β and Tumor Necrosis Factor- α (TNF- α) in bladder cells (3-5).

Some in vitro studies demonstrated that lactobacilli produce mucin, biosurfactant barrier and bacteriocin. They compete for receptors on uroepithelium thus avoiding the adhesion of pathogens. They have been shown to decrease inflammatory cytokines such as IL-8 and COX or expression of virulence factors. They also increase immune system response via IgA, IL-10 and IL-12.

Lactobacillus acidophilus (*L. acidophilus*) has been shown to inhibit *E. coli* in vitro by prevention of adhesion and producing H₂O₂ and biosurfactant. *Lactobacillus rhamnosus* GR-1 attached to uroepithelium and avoided the growth and adhesion of uropathogens. *Lactobacillus reuteri* RC-14 avoided uropathogen adhesions with H₂O₂ and biosurfactant. *Lactobacillus casei* in the bladder of animals was proved to be very successful in the eradication of 84% of the uropathogens by stimulating immune response and natural killer cells (6).

Another probiotic, which contains *E. coli* Nissle 1917 was analyzed and shown to be useful for prevention of pediatric UTIs by its microcin effect and rapid growth rate as the uropathogens mostly arrive from the gut (7).

Another study found that lactic acid, H₂O₂ and *Lactobacillus* in culture supernatants inhibited growth, increased promoter activity of outer membrane proteins of the host and downregulated type 1 and P fimbriae of *E. coli* that have a role in attachment of uropathogens (8).

Downregulation of proinflammatory cytokines such as Interleukin (IL)-6, IL-8, IL-10, IL-12 and TNF- α was possible with *L. rhamnosus* GR-1 and *L. reuteri* RC-14. Antiinflammatory results were observed both in serum and urine samples of the patients. The UTI symptoms can also be managed easily as a result of the downregulation of these cytokines (9).

Consumption of *L. gasseri* and *L. coryniformis* increased natural killer cells and IgA concentrations of the host (10).

Immunomodulatory proteins produced by *L. rhamnosus* GR-1 were found to strengthen the activity of nuclear factor-kappa B (NF- κ B) in *E. coli*-stimulated bladder cells. Nuclear factor- κ B is a transcription factor that regulates

immunological genes. This method has been shown to enhance the clearance of uropathogens and used for prevention and treatment of UTI, which may also be valuable if live bacteria are not preferred to be used (11).

In vitro activity of commercial Lactocabilli may also help maintain a balanced urogenital flora, displace uropathogenic *E. coli* (UPEC) and reduce UTI rates. They upregulated antimicrobials, inhibited growth with acids and reduced survival of pathogens. Lactic acid was measured at high amounts, and reduced pH, permeabilized outer membranes of bacteria, had chelating effects and inhibited growth by capturing nutrients such as iron (12).

4. Trials on the Current Concept

Probiotics have been used in observational studies in several countries for 20 years and found to be safe and efficient in thousands of adults and infants (2).

In a randomized, double-blind placebo controlled study, oral intake of probiotics containing *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 were shown to reduce pathogen load in the urogenital tract (13).

A prospective randomized controlled trial, with 120 children having persistent Vesicoureteral Reflux (VUR) for one year given *L. acidophilus* (2×10^8 CFU/day) or low dose trimethoprim/sulfamethoxazole prophylaxis and probiotics, found that these combinations were as effective as antibiotic prophylaxis and much more effective than a previous report including children with no prophylaxis (6).

Breastfeeding as a natural probiotic has been shown to prevent UTI in 200 infants in a case controlled study. As duration of breastfeeding increased, risk of UTI decreased significantly (14).

Urinary Tract Infection rates were found to be less frequent in a double-blind study with 585 preterm infants given *Lactobacillus* GG compared to the placebo group in neonatal intensive care unit (15).

There are also other reports of efficient prophylaxis with probiotics such as *L. acidophilus* capsules in pediatric recurrent UTIs (16).

In a small study on ten adult females with recurrent UTI, probiotic preparation containing 10^9 CFU of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 was given orally to the patients twice daily for two weeks. Infection parameters resolved one week after this treatment in six of the cases (17).

In a double-blind multicentre trial including 252 postmenopausal females with recurrent UTIs, oral prophylaxis was given either with trimethoprim / sulfamethoxazole or 10^9 CFU of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 two times a day, for one year. Probiotic and antibiotic prophylaxis were found similarly successful in reducing UTI recurrence, yet

the group receiving probiotic had the advantage of not experiencing resistance (18).

Lactobacillus rhamnosus GR-1 and *L. reuteri* RC-14 were also shown to protect the urogenital tract from UPEC colonization and infection on experimental cultures (8).

In a preliminary randomized controlled trial with 85 children aged 3 to 15 years, who had recurrent UTI and unilateral VUR, one group was given prophylactic nitrofurantoin and the second group was given nitrofurantoin and probiotic (*L. acidophilus* and *Bifidobacterium lactis* 10^7 CFU/mL) together for a certain period intermittently during more than a year. Follow up continued for two to three years and both groups had similarly decreased incidence of UTI. However, nitrofurantoin together with probiotics was found to be more effective in reducing febrile UTIs (19).

Among 600 samples of urine infected with $> 10,000$ CFU/mL multidrug resistant bacteria, *Lactobacilli* probiotics (*L. acidophilus*, *L. casei* and *L. rhamnosus*) did not have antagonistic effect on tests with *Enterococcus*, *Enterobacter* or *Klebsiella pneumoniae*. However, probiotics had an inhibitory effect on *E. coli*. Moreover, *L. casei* was the most effective bacteria (20).

Three hundred and forty-four children aged three months to 12 years receiving broad-spectrum antibiotics in PICU were administered a probiotic mixture containing *L. acidophilus*, *L. rhamnosus*, *Bifidobacterium bifidum*, *B. longum*, *Saccharomyces boulardii* and *Streptococcus thermophilus* for seven days. Prevalence of candidemia and candiduria was successfully reduced with probiotics compared to the control group of 376 children not taking probiotics (21).

Overall, 5×10^9 CFU of *S. boulardii* either in capsule or powder form was administered orally to 24 children aged 3 to 16 years for five days. Number of *E. coli* colonies in colon was measured before and after treatment. In children's analyzed stool samples, *E. coli* colonization was found to be decreased. Therefore, prevention of UTIs can be possible using *S. Boulardii* (22).

In vitro effect of single and multi-strain probiotics on *E. coli* and *Enterococcus faecalis* as urinary tract pathogens was tested. The probiotic mixtures used were two *lactobacilli* (*L. acidophilus* and *L. plantarum*), three *lactobacilli* (*L. acidophilus*, *L. fermentum* and *L. rhamnosus*), four *lactobacilli* (*L. acidophilus*, *L. fermentum*, *L. rhamnosus* and *L. plantarum*) and a commercial mixture. It consisted of *L. acidophilus*, *L. delbrueckii*bulgaricus, *L. casei*, *L. plantarum*, *L. rhamnosus*, *L. salivarius*, *L. helveticus*, *L. lactis*, *B. bifidum*, *B. breve*, *B. infantis*, *B. longum*, *S. thermophilus* and *Bacillus subtilis*. Probiotics as single and in combination forms were equally effective on preventing uropathogen growth and reducing UTI risk (5).

A retrospective study compared the effectivity of prophylaxis with probiotics (*L. acidophilus* 1×10^8 CFU/g or

L. acidophilus + *L. rhamnosus* 2×10^9 CFU/g), antibiotics (trimethoprim/sulfamethoxazole) and no-prophylaxis in three groups. There was a total of 191 infants, who had acute pyelonephritis and anatomically normal urinary tracts. Incidence of UTI for six months after pyelonephritis was investigated. Probiotics were significantly more effective for prophylaxis than no-prophylaxis. Although not statistically significant, probiotics also resulted in lower UTI rates than the antibiotic group. The resistance rates of *E. coli* were much lower in the probiotic group than in the other two groups (23).

However, there are some rare reports that probiotics may lead to serious infections both in immunocompetent and immunocompromised patients and the detection of causative agent is difficult as they are usually regarded as contaminants. An adult, who had diverticulosis and hemorrhoidal bleeding was reported to have *L. casei* bacteremia treated successfully with antibiotics (24).

One term newborn with multiple congenital anomalies and one extremely preterm newborn had sepsis due to 5×10^9 CFU oral *L. rhamnosus* GG supplementation given to avoid antibiotic associated complications or necrotizing enterocolitis. There are also other adult or pediatric cases of bacteremia, sepsis, fungemia, infectious endocarditis, pneumonia, chorioamnionitis, meningitis, UTI and abscesses due to probiotics like *lactobacillus*, *bifidobacterium* and *saccharomyces*. The majority of these case reports have a serious or chronic disease such as gastrointestinal pathology, prematurity, diabetes, heart defect, cerebral palsy, burn, recent surgery or immunosuppression due to several reasons. However, these should not discourage the use of probiotics as the number of these cases are much lower than the great population that benefits from probiotics. The important point is that clinicians should keep in mind that these agents may cause serious infections especially in certain patient groups, who have underlying health problems (25-27).

5. Recommended Dosages and Duration

There is a wide range of dosage and duration choices regarding probiotic administration depending on patient's age, clinical status and clinician's perspective. The dose of *Lactobacillus rhamnosus* was reported to range from 3×10^9 CFU, 5×10^9 CFU to 10×10^9 CFU and duration of supplementation differed from 4 to 169 days. Other trials recommended the dosage of *Lactobacillus* species and *Bifidobacterium* species ranging from 1×10^9 CFU in children to 35×10^9 CFU in adults depending on preparation and duration of up to six weeks. *Saccharomyces boulardii* dose has been recommended as 250 mg to 500 mg (4, 28).

6. Conclusion

Efficacy and safety of probiotics for UTIs have been investigated and shown promising results. Probiotics may be promising and effective natural immunomodulators for prevention and treatment of UTIs in children. There is sufficient data to suggest that this approach is a valuable choice that should be encouraged regarding its utilization in UTIs and benefits from all of the advantages simultaneously.

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Footnotes

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