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Gastroenterology

Probiotics – focus on women and children

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Introduction

The early history of probiotic development and their role in women's health started in the mid-1970s, when it was observed that women who had never had a urinary tract infection (UTI) were colonised in the vagina by lactobacilli, whereas women with recurrent UTIs were colonised by the coliforms that ascended into and infected the bladder.[1] While some researchers focused on *Escherichia coli's* role in the pathogenesis of UTI, others investigated the health-orientated lactobacilli. Some of these research efforts are now providing health benefits, particularly in women prone to UTIs.

LEARNING OBJECTIVES

You will learn:

- The latest evidence on probiotic's value in women's health focussing on urinary tract infections and vaginal flora
- Understand the role of probiotics in:
  - reducing antibiotic use
  - acute otitis media of childhood
  - reducing bouts of diarrhoea in children
  - antibiotic prescribing for common infections in childhood.

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Why is there such an interest in probiotics and community-acquired UTIs?

Community-acquired bacterial UTI is common, affecting up to 60% of women at some point in their lifetime. UTIs are classified according to severity, anatomical levels, how acquired (e.g. catheter-related) and whether they are initial, persistent or recurrent (Figure 1).[2] Uncomplicated UTIs are symptomatic when there are clinical urinary symptoms that indicate infection, such as dysuria, urinary frequency and urgency. The presence of pathogens verified by a positive urine dipstick test can help to confirm diagnosis. A negative result in a highly symptomatic woman cannot rule out the diagnosis of a bacterial infection. In women, urine culture is not required in suspected acute uncomplicated cystitis because the spectrum of causative organisms is predictable.

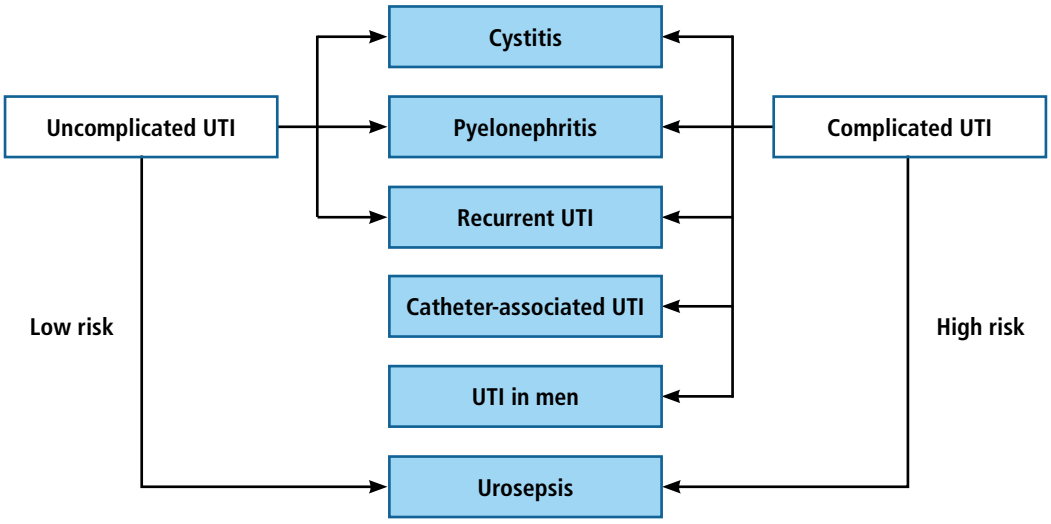

Figure 1. Uncomplicated and complicated UTIs[2]

The following classification of UTIs is drawn from the EAU Urological Infections Guidelines.

Table 1. Classification of UTIs

Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, premenopausal women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities
Complicated UTIs	All UTIs that are not defined as uncomplicated, meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course, i.e., all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases, e.g. diabetes
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months
Catheter-associated UTIs	Catheter-associated UTIs are those occurring in a person whose urinary tract is currently catheterised or who has had a catheter in place within the past 48 hours
Urosepsis	Urosepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, originating from the urinary tract and/or male genital organs

Major international guidelines recommend short-term oral antibiotics for the treatment of uncomplicated UTIs (Table 2), but increasing concerns about antimicrobial resistance and the use of multiple antibiotics to treat bouts of UTI in an individual patient have led to greater interest in the use of probiotics and other immune-boosting therapies.

A recent South African (2013) study of the antimicrobial susceptibility of organisms causing community-acquired UTIs in Gauteng[3] has shown high susceptibility profiles for fosfomycin, nitrofurantoin and cefuroxime. Trimethoprim/sulfamethoxazole combination therapy was the least efficacious antimicrobial agent. UTI pathogens were susceptible to the fluoroquinolones (94%; CI 90.8-97.4), but these agents are not recommended internationally for uncomplicated UTIs.

Table 2. Suggested regimens for antimicrobial therapy in uncomplicated cystitis in women

Antimicrobial	**Daily dose**	**Duration of therapy**
Fosfomycin trometamol	3g SD	1 day
Nitrofurantoin macrocrystal	50-100mg 4 times/day	5 days
Pivmecillinam	200mg/day	3-5 days
Alternatives	**Daily dose**	**Duration of therapy**
Cephalosporins (e.g. cefuroxime, cefixime)	500mg BID	5 days
Do not use fluoroquinolones to treat uncomplicated cystitis		

Do oral probiotics help to reduce symptoms and recurrences of UTIs?

The latest European guidelines suggest that *Lactobacillus* spp. may be useful, as individual studies have shown that oral lactobacilli probiotics do reach and influence the vaginal flora biome.[2,4] The use of probiotics, D-mannose and cranberry products in combination can be of value in reducing symptoms and recurrences of UTIs, but high-level evidence is still awaited.

There is certainly increasing interest in using non-antibiotic therapy for UTIs. This is evident from the dramatic increase in published studies. Pubmed searches in 2000 for the topic 'probiotics and urinary tract infection' showed only five studies, while in the last 15 years, some 174 studies have been published. It is hoped that this greater research interest will yield further substantive data for clinical action.

Probiotics and children

The infant gut contains very few or no species of microbes at birth; during the birth process, either vaginal or caesarean, development of the gut microbiome is initiated and subsequently alters with exposure to breast-feeding, infant milk formulas, different foods, the environment and treatment of childhood illnesses with antibiotics and other medications. Up to the first two years of life, the composition of the gut microbiome often varies. After two years, when children are starting to eat a more varied complex diet (e.g. fibres and complex carbohydrates), the gut microbiome becomes more diverse and stable (Figure 2).[5]

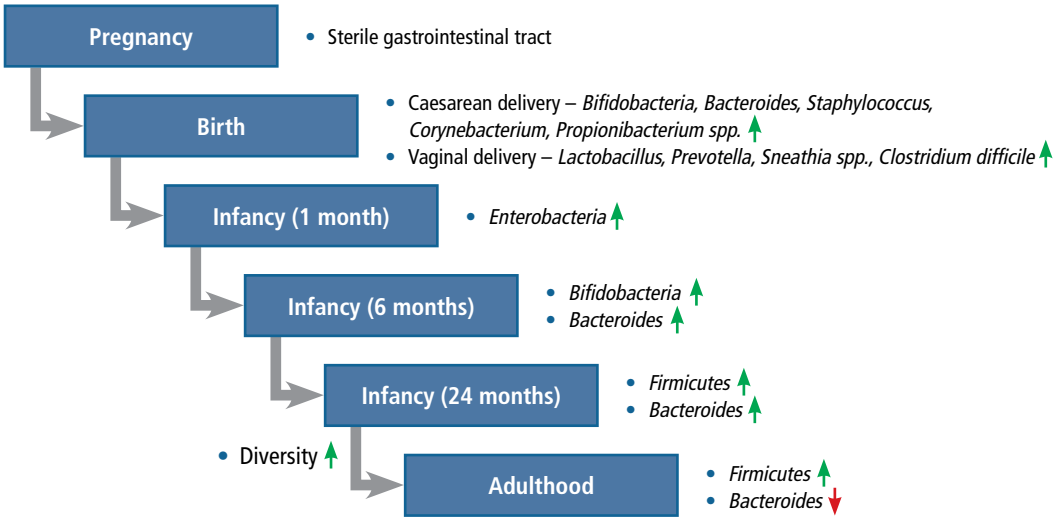

Figure 2. Development of the gut microbiome

The study showed the safety of early exposure to B. lactis in immunologically at-risk infants in respect of normal weight gain and anthropometric measurements of growth

With the decline in breast-feeding and increasing early medical intervention using antibiotics to treat childhood illnesses, interest in maintaining a healthy gut microbiome in childhood has increased, leading to the early development of probiotic-containing infant formulas, other foodstuffs containing *Lactobacillus* spp. and probiotic medical formulations for toddlers and young children. Increasing antibiotic resistance and efforts to reduce antibiotic use in early childhood have spurred further interest in the benefits of probiotics, which can be defined as 'live, beneficial bacteria'.

Safety of probiotics in infancy

Early benefits of a starter formula with pre- and probiotics in South African babies born to HIV-positive mothers

In a double-blind study[6] of HIV-positive mothers on antiretroviral therapy during pregnancy who elected not to breast-feed their babies, more than 400 babies were given either a standard formula or a formula enriched with probiotics (cow's milk-derived oligosaccharides) and the probiotic *Bifidobacterium animalis subsp. lactis* (*B lactis*). The safety of the formula was evaluated, as were the bifidobacterial levels in the gut of the infants born vaginally or via caesarean section. The primary efficacy outcome was faecal bifidobacterial count at 10 days and the primary safety outcome was daily weight gain between 10 days and four months.

Importantly, this Wits University study showed that the probiotic formula was safe and well tolerated in these immunologically at-risk infants. In addition, the bifidobacterial count increased at 10 days, 28 days and 84 days after birth in the infants fed probiotic-containing formula, compared to those on the standard formula. Notably in caesarean-born infants, *Bifidobacterium* levels were restored to the same levels as those of infants born vaginally within three days of their ingesting the supplemented formula. In the vaginally delivered group, *Bifidobacteria* increased over three months of life and *Lactobacillus* spp. were present at three months.

The study showed the safety of early exposure to *B. lactis* in immunologically at-risk infants in respect of normal weight gain and anthropometric measurements of growth.

Probiotics for preventing acute otitis media (AOM) in children

Acute middle ear infection is one of the most common childhood diseases and the most common reason for prescribing antibiotics in this age group. Many clinical guidelines recommend antibiotics as first-line therapy for severe AOM. It is for this reason that preventing AOM is a useful objective in medical strategies seeking to lower early exposure to antibiotics in childhood.

A recent Cochrane review of 17 randomised clinical trials (3 488 children), 11 of *Lactobacillus*-containing probiotics and six of *Streptococcus*-containing probiotics, highlighted the evidence-based benefits.[7] In children prone to AOM, probiotic use reduced the number of episodes, but in children experiencing an incidental AOM (i.e. those not particularly prone) there was no clear benefit. Reduced scripting of antibiotics was seen in all children on probiotic treatment (Table 3).

Caution is recommended when prescribing probiotic formulations to severely immune-compromised children

Table 3. Evidence-based benefits of probiotics preventing bouts of AOM

Episodes of AOM in prone children	Reduced episodes in probiotic-treated children (NNTB*=10)
In non-prone AOM children	No significant benefit
Severity of AOM	Not accessed
Percentage taking antibiotics for any infection	Fewer antibiotics were prescribed in probiotic-treated children (NNTB=8)

**NNTB: number needed to treat to benefit*

Probiotics for the prevention of paediatric antibiotic-associated diarrhoea (AAD)

Antibiotics alter the microbial balance in the gut and this frequently leads to diarrhoea. Probiotics may help to prevent AAD by protecting against or correcting 'leaks' in the gut barrier and restoring gut microflora.

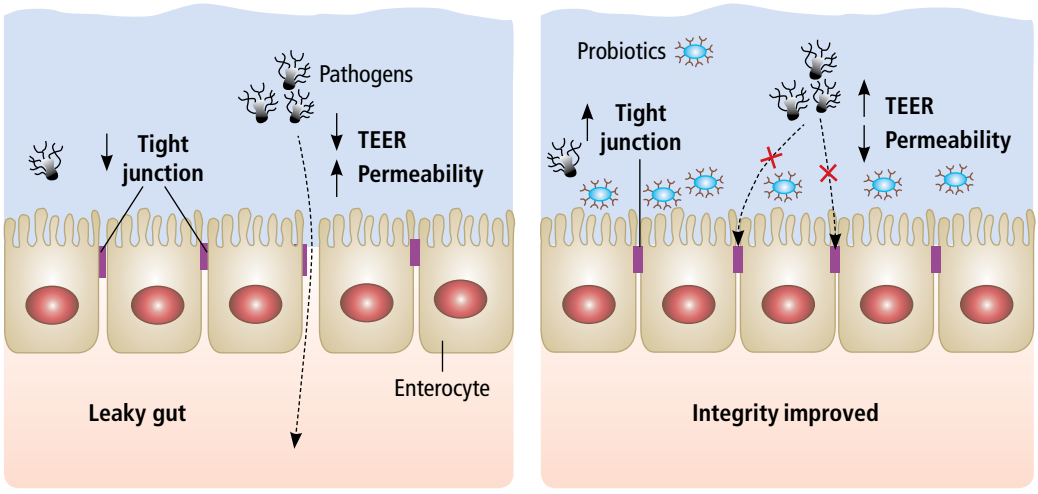

Figure 3. Modulation of intestinal barrier function by probiotics [8]

This review of published data focused primarily on *Bifidobacterium* spp., *Lactobacillus* spp. and some *Streptococcus* spp., alone or in combination.[9] The main findings were:

- After five days to 12 weeks of follow-up, the incidence of AAD in the probiotic group was lower than in the control group (there were some 6 000 participants)
- High-dose formulations (>5 billion colony-forming units (CFUs)) were more effective than lower-dose probiotic formulations
- In children on a lower dose (<5 billion CFUs), the NNT to prevent one case of diarrhoea was 20
- Reduction in duration of diarrhoea was modest (one day)
- Caution is recommended when prescribing probiotic formulations to severely immune-compromised children.

Probiotics for preventing *Clostridium difficile*-associated diarrhoea (CDAD) in children

Antibiotic use may also lead to reduced resistance to pathogens such as *C. difficile*.

In a recent Cochrane review, the risk of developing CDAD was reduced on average by 60% when probiotics were given with antibiotic therapy. The most common side effects of probiotic use in this setting were abdominal cramping, nausea, fever and taste disturbance.[10]

KEY LEARNINGS

- Oral antibiotics are recommended for the treatment of uncomplicated UTIs
- Increasing interest in reducing antibiotic use for this common bacterial infection in women has led to a focus on oral probiotic use
- Evidence that oral probiotics reach and influence the vaginal flora are encouraging their use to reduce frequent bouts of UTIs
- A recent Cochrane review has highlighted the benefits of probiotics in reducing episodes of acute otitis media in children. Probiotic use was associated with fewer antibiotic prescriptions for any infections in treated children
- Probiotics help to restore the so-called 'leaky gut' caused by antibiotics. In children, probiotic use was associated with fewer bouts of diarrhoea. The number needed to treat (NNT) to prevent one case of diarrhoea was 20.

This CPD accredited programme was written for *deNovo Medica* by
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