

Practical Insights: Probiotics and AAD



Diarrhoea is a common adverse effect of antibiotic treatments. **Antibiotic associated diarrhoea (AAD) occurs in about 5-30% of patients between the initiation of therapy and up to 2 months after cessation of treatment.** Clinical presentations of AAD range from mild diarrhoea to fulminant pseudomembranous colitis. The latter is characterized by watery diarrhoea, fever (in 80% of cases), leucocytosis (80%), and the presence of pseudomembranes on endoscopic examination. Severe complications include toxic megacolon, perforation and shock.

Almost all antibiotics, particularly those that act on the anaerobes, can cause AAD, but the risk is higher with aminopenicillins, a combination of aminopenicillins and clavulanate, cephalosporins and clindamycin. Host factors for AAD include age over 65, immunosuppression, being in an intensive unit, and prolonged hospitalization.

***Clostridium difficile* has been recognized as the major enteropathogen of AAD. It is responsible for 10-25% of cases of AAD and for virtually all cases of pseudomembranous colitis.** It works by secreting two potent toxins that cause mucosal damage and inflammation of the colon.

Treatments and Drugs

In mild to moderate diarrhoea, conventional measures include rehydration or discontinuation of the inciting agent or its replacement by an antibiotic with a lower risk of inducing diarrhoea, such as quinolones, co-trimoxazole or aminoglycosides. In cases of severe or persistent AAD (pseudomembranous colitis), drug therapy with Metronidazole or Vancomycin is usually prescribed. Both antibiotics effectively control *C. difficile* with a response rate of >90% and diarrhoea resolving in two to three days.

Probiotics

As AAD mostly results from a disequilibrium of the normal intestinal flora, research has focused on the benefits of administering living organisms – probiotics, to restore the normal flora. Numerous probiotics such as *Lactobacillus acidophilus*, *L. casei* GG, *L. bulgaricus*, *Bifidobacterium bifidum*, *B. longum*, *Enterococcus faecium*, *Streptococcus*

thermophilus, and *Saccharomyces boulardii* have been tested for the treatment and prevention of AAD. Whilst some studies have shown good results for probiotics like some *Lactobacillus spp.*, others are conflicting due to the small and open trials of treatment. Nonetheless, *S. boulardii* has shown promising results, which we will discuss in-depth in the next section.

Saccharomyces boulardii

S. boulardii was first isolated from lychee fruit in Indochina and used in France to treat diarrhoea, beginning in the 1950s. **It is a non-pathogenic yeast which possesses many properties that make it a potential probiotic agent – it survives transit through the GI tract, it has an unusual optimal growth temperature of 37°C, it reaches high concentrations in the colon quickly, does not permanently colonize the colon and does not translocate easily out of the intestinal tract.**

Many meta-analyses of controlled trials have demonstrated the efficacy of *S. boulardii* in the prevention of AAD. In 2002, D'Souza et al reported that *S. boulardii* significantly lowered the risk of AAD by 60% as compared to the placebo. Later studies by Szajewska et al in 2005 and McFarland in 2006 concluded the same reduction in relative risk of AAD in patients treated with *S. boulardii* and antibiotics.

Interestingly, ***S. boulardii* is the only probiotic which has shown effectiveness in *C. difficile*-associated diarrhoea (CDD).** In a randomized, placebo-controlled study of *S. boulardii* in combination with Vancomycin or Metronidazole for patients with CDD, 50% reduction of recurrences was observed in patients who had a history of at least one prior CDD episode.

The clinical benefits of *S. boulardii* could be explained by its mechanisms of action: (i) production of factors that neutralized bacterial toxins, (ii) modulation of the host cell signaling pathway implicated in proinflammatory response during bacterial infection, (iii) release in vivo of substances that inhibit certain bacterial toxins and/or their pathogenic effects, (iv) trophic effects, (v) antisecretory activity and immunostimulatory effects on the intestinal mucosa, and (vi) anti-inflammatory effects.

Moving On...

The ease of administration, cost effectiveness, and the relative lack of side effects, makes probiotics a viable option in preventing AAD. Although more controlled clinical trials are needed before probiotics can be routinely prescribed with concurrent antibiotics therapy, the efficacy of some, especially *S. boulardii*, cannot be underestimated!

Quick Facts

Effects of probiotics are strain-specific. A strain that is effective in the GI tract may not be as effective in the genitourinary system, or vice versa.

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Think BIG,
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Greetings from the Editor

The word “Women” may have crossed your mind by the look of this issue. Yes indeed in this third issue, we embark on a journey to discover the role of probiotics for women health.

Urogenital infections afflict an estimated one billion women each year. The size of this problem and the increased prevalence of multi-drug resistant pathogens make it imperative that alternative remedies be found. Recent studies have emphasized the importance of a healthy, lactobacilli dominated flora not only to prevent sexually transmitted disease and preterm labour but also to maintain the quality of life of women. Dr KK Chow's article takes you to the role of probiotics in women urogenital healthcare.

Adding on, we have also for you, an interesting article on how probiotics may assist women regain their figures after pregnancy.

Not forgetting the Practical Insights section, the use of probiotics for the prevention of antibiotic associated diarrhoea is discussed.

In conclusion, we would like to extend our heartfelt appreciation to Dr KK Chow for his inclusion in this issue of the newsletter despite his busy work schedule.

Thank you & God Bless!

Melvin Wong

Editor-in-Chief

Probiotics in Urogenital Health

by **Dr Chow Kah Kiong**

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I remember as a young boy, while encouraging me to be a doctor, my father – a Western-trained doctor, would always see a Traditional Chinese Medicine practitioner for his simple ailments. Many times, he would tell me that the herbal mixture given to him to boil and drink by the *Sinseh* was a well balanced concoction, which helps balanced the ‘yin’ and ‘yang’ in our body and does not upset the body's natural strength. It uses our body's ability to get rid of introduced particles of infection or injury. Therefore, it was that much easier for me to embrace the concept of probiotics when I was introduced to it.

What are Probiotics?

The concept of probiotics dates back more than 100 years. The idea arose from the realization that humans are inhabited with microbes from birth and that these organisms play a role in preventing diseases by restoring normal flora or microbiota of the body or its organ(s), improving its wellbeing and helping it resist or recover from infections.

Most of the research on probiotics has focused on intestinal benefits of lactic acid bacteria. Recently, a much broader definition of “**Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host**”, allows the expansion and recognition of the use of probiotics for urogenital diseases.

The Lactobacillus

In common female urogenital infections, probiotics are expected to enhance the body's natural defenses as they foster the growth of the healthy resident microorganisms to restore or maintain the delicate balance. The bacteria identified and studied so far are mainly the species of *Lactobacillus* which acidify the vagina, inhibiting the growth of invading pathogens.



The Döderlein (Lactobacilli) flora is named after the Munich gynaecologist, Albert Döderlein who discovered its existence in the vaginal flora of healthy women in 1892. It is composed of a mixture of 10 to 20 types of Lactobacillus bacteria. Döderlein observed that the Lactobacillus bacteria produced lactic acid, which prevents an overgrowth of pathogenic bacteria by forming a protective biofilm at the surface of the vaginal mucosa. Thriving on glycogen stores produced by the vaginal mucosa after puberty, the Lactobacillus bacteria growth is directly affected by estrogen levels.

Low estrogen levels significantly reduce the available glycogen, inhibiting *Lactobacillus* growth and therefore, increase the risk of bacterial vaginal infections. High estrogen levels, while important to control the pathogenic bacteria growth, may favour an overgrowth of *Candida* leading to a yeast infection, since *Candida* also grows on glycogen. Oral contraceptives with high estrogen levels or the use of antibiotics that destroy healthy vaginal flora, both contribute to candidiasis.

After menopause, some 25% to 30% of women still have lactobacilli present, and this number rises to between 60% and 100% with the use of vaginal or oral estrogen-replacement therapy. Correspondingly, rates of vaginal infections and even urinary tract infection (UTI) increase with age and decrease with estrogen-replacement therapy.

The Common Urogenital Infections in Women

Vulvovaginitis is one of the most common problems in clinical medicine today, and probably the most common reason why women visit their gynaecologists. It causes vaginal discharge, irritation, and itching. Affecting women of all ages, it is an inflammation of the vagina and vulva, most often caused by bacterial (e.g. *Gardnerella*, Group B streptococci), fungal (usually *Candida*), or parasitic (*Trichomonas*) infection, in that order of incidence. Respectively, they are termed bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) and trichomoniasis.

With the exception of trichomoniasis, **the root cause of most of these vaginal infections is an imbalance or alteration of the vaginal flora.** This probably explains why many women are plagued with recurrent vaginal infections for no apparent reason. It also explains the fact that in BV and VVC, the women could be absolutely asymptomatic and "disease free" while harbouring the very organisms in their vagina, indicating the situation whereby these organisms are well contained in the normal flora of these patients. *G. vaginalis* can be recovered from the vagina in 30-50% of asymptomatic women.

The same is observed in UTI in women. The higher incidence of recurrent UTI (referring to those with no associated urinary pathology) seen in women could also be related to altered vaginal and intestinal flora, especially in postmenopausal women with atrophic vagina. Their low estrogen levels and the lack of normal vaginal lactobacilli make them more vulnerable to infections. Similar normal flora alterations during the first few sexual intercourse could also be a contributing factor in 'honeymoon cystitis', other than the initial trauma to the external urogenital region. This may also explain why

many of the UTIs are due to bacteria found asymptomatically in the lower intestine and the vagina.

Studies have also shown that the **absence or depletion of lactobacilli in the vagina associated with overgrowth of anaerobic pathogens causing BV, results in significantly increased risk for HIV, as well as gonorrhoea, chlamydia, and herpes simplex virus infections.** By mechanisms not yet understood, BV displaces lactobacilli, elevating vaginal pH and creating an environment within which the pathogens survive and can infect the host.

The Role of Probiotics in Urogenital Infections

BV, VVC and Recurrent UTI by their characteristics seem to fit well into the concept of probiotics treatment. In BV and VVC, micro-organisms such as *G. vaginalis* and Group B streptococci (in BV) and *Candida albicans* (in VVC), at times can colonize the vagina asymptotically, while at other times cause severe irritation and discharge. This is probably due to some imbalance in or lack of effect of the co-existing normal flora, especially the Lactobacilli species. Furthermore, the lack of endogenous estrogen and the administration of exogenous estrogen can alter the Lactobacillus bacteria in the vagina, leading to BV or VVC. The common bacteria causing BV and UTIs are asymptomatic commensals (sometimes transient or passing) in the lower intestinal tract.

All these tend to indicate the potential of introducing live organisms of the *Lactobacillus* species into the vagina via the intestinal tract to prevent, reduce or even treat such infections. However, more than this, scientists have been gathering direct evidence that administering probiotics orally or vaginally could alter or boost the vagina flora in the treatment of these urogenital infections. A few well-controlled, though small, studies seem to have shown positive results.

The Right Strains

After the commercial introduction of *L. casei* Shirota (*Yakult*) in Japan in the 1930s, the next probiotic strains to be discovered and extensively studied were *L. acidophilus* NCFM (mid-1970s) for the gut and *L. rhamnosus* GR-1 and *L. fermentum* (presently called *L. reuteri*) RC-14 for the urogenital tract (1980 through 1985). Since then, several research groups have attempted to identify suitable candidates for vaginal colonization.



Not all lactobacilli possess properties that are required to colonize the vagina and inhibit urogenital pathogens. Among all, *L. rhamnosus* GR-1 and *L. reuteri* RC-14 have emerged with excellent clinical potential for the urogenital tract.

L. rhamnosus GR-1 is highly adherent to urogenital and vaginal cells, resistant to spermicide, able to inhibit growth and adhesion of urogenital and intestinal pathogens, and able to colonize the vagina and intestine. *L. reuteri* RC-14 is an adherent strain that produces hydrogen peroxide and a highly potent biosurfactant, and it also colonizes the vagina and the intestine. An important component of *L. reuteri* RC-14's anti-infective capacity is its biosurfactant, which inhibits adhesion of a range of uropathogens, including *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, Group B streptococci, *Pseudomonas stuartii*, and *Staphylococcus epidermidis*, and the genital pathogens *C. albicans*, and *G. vaginalis*.

Research Studies on Probiotics in Urogenital Infections

Dr Gregor Reid of the Department of Microbiology and Immunology, University of Western Ontario and Canadian Research and Development Centre for Probiotics, Lawson Health Research Institute, is the leading scientist in this area of research. Most of the randomized controlled studies in the field of probiotics in urogenital infections are the results of his work.

His team in 2003 had shown that oral *L. rhamnosus* GR-1 and *L. reuteri* RC-14 significantly altered vaginal flora by increasing Lactobacillus count and reducing yeast count in a randomized, placebo-controlled trial of 64 healthy women.

Earlier in 2001, they showed that the oral introduction of lactobacilli could provide a significant probiotic effect. Using the strains *L. rhamnosus* GR-1 and *L. reuteri* RC-14 suspended in skim milk and given twice daily for 14 days in 10 women with a history of recurrent yeast vaginitis, BV and UTIs, these micro-organisms were recovered from the vagina and identified by morphology and molecular typing within 1 week of commencement of therapy. Moreover, within that study group, six cases of asymptomatic BV resolved within 1 week of therapy.

In 2006, Anukam et al showed in a randomized, double-blind, placebo-controlled trial on 125 premenopausal women that the use of these same micro-organisms as a probiotic, augmented the metronidazole treatment of BV.

Probiotics in Clinical Practice

For the general practice physician, it is difficult to apply probiotic concepts to patient care because products especially designed for female urogenital health are still limited. Moreover, in many women, the imbalance in her vaginal flora that contributes to urogenital infections seems to self-correct on a regular basis for reasons not yet understood. At the same time, there are those whose asymptomatic condition progresses to a symptomatic one requiring treatment while the flora remains unchanged.



Sobel found that while probiotics may help in BV, it has little impact in VVC. This could be explained by the fact that in Candidiasis there could be enough of lactobacilli in the vagina as it is mostly associated with conditions of increased glycogen in the vagina.

Many so-called probiotic products currently on the market have never been proven, using acceptable methods, to have health benefits; indeed, many have been found to either contain dead organisms or species that are different from those stated on the label. Furthermore, some less credible marketing companies make outlandish or subtly incorrect claims in their publicity material, including content placed on Web sites. As a result, the concept of probiotics has lacked credibility in the medical community and many consumers have purchased and used unreliable products. But a broadening of education about probiotics spurred on by good science and rigorous clinical studies are changing perceptions in the medical community about probiotics. (For example, a recent Medscape Medical News CME program examined the safety and tolerability of probiotics added to infant formula.)

Present and Future

Urogenital infections not caused by sexual transmission, namely Vulvovaginal Candidiasis, Bacterial Vaginosis, and Urinary Tract Infection remain a major medical problem in terms of the number of women afflicted each year. Although antimicrobial therapy is generally effective at eradicating these infections, there is still a high incidence of recurrence. The patient's quality of life is affected and many women become frustrated by the cycle of repeated antimicrobial agents whose effectiveness is diminishing due to increasing development of microbial resistance.

"There is good clinical evidence to show that the intestinal and urogenital microbial flora have a central role in maintaining both the health and wellbeing of humans. Furthermore, the use of 'good bacteria' to replace or augment bacterial populations is gradually achieving some scientific acceptance." Reid.

The role of the intestinal, vaginal, and urethral flora and probiotics in urogenital health should be the focus of further research and studies. Meanwhile, its clinical use should be selective and closely monitored.

NEWS RELEASE

ECO 2009 – The 17th European Congress on Obesity Amsterdam 6-9 May 2009

Study in pregnant women suggests probiotics may help ward off obesity

Amsterdam, the Netherlands: One year after giving birth, women were less likely to have the most dangerous kind of obesity if they had been given probiotics from the first trimester of pregnancy, found new research that suggests manipulating the balance of bacteria in the gut may help fight obesity.

Probiotics are bacteria that help maintain a healthy bacterial balance in the digestive tract by reducing the growth of harmful bacteria. They are part of the normal digestive system and play a role in controlling inflammation. Researchers have for many years been studying the potential of using probiotic supplementation to address a number of intestinal diseases. More recently, obesity researchers have started to investigate whether the balance of bacteria in the gut might play a role in making people fat and whether adjusting that balance could help.

“The results of our study, the first to demonstrate the impact of probiotics-supplemented dietary counselling on adiposity, were encouraging,” said Kirsi Laitinen, a nutritionist and senior lecturer at the University of Turku in Finland who presented her findings on Thursday at the European Congress on Obesity. **“The women who got the probiotics fared best. One year after childbirth, they had the lowest levels of central obesity as well as the lowest body fat percentage.”**

"Central obesity, where overall obesity is combined with a particularly fat belly, is considered especially unhealthy," Laitinen said. "We found it in 25% of the women who had received the probiotics along with dietary counselling, compared with 43% in the women who received diet advice alone."

In the study, 256 women were randomly divided into three groups during the first trimester of pregnancy. Two of the groups received dietary counselling consistent with what's recommended during pregnancy for healthy weight gain and optimal foetal development. They were also given food such as spreads and salad dressings with monounsaturated and polyunsaturated fatty acids, as well as fibre-enriched pasta and breakfast cereal to take home. One of those groups also received daily capsules of probiotics containing *Lactobacillus* and *Bifidobacterium*, which are the most commonly used probiotics. The other group received dummy capsules. A third group received dummy capsules and no dietary counselling. The capsules were continued until the women stopped exclusive breastfeeding, up to 6 months.

The researchers weighed the women at the start of the study. At the end of the study they weighed them again and measured their waist circumference and skin fold thickness. The results were adjusted for weight at the start of the study.

Central obesity - defined as a body mass index (BMI) of 30 or more or a waist circumference over 80 centimetres - was found in 25% of the women who had been given the probiotics as well as diet advice. That compared with 43% of the women who got dietary counselling alone and 40% of the women who got neither diet advice nor probiotics. The average body fat percentage in the probiotics group was 28%, compared with 29% in the diet advice only group and 30% in the third group.

Laitinen said further research is needed to confirm the potential role of probiotics in fighting obesity. One of the limitations of the study was that it did not control for the mothers' weight before pregnancy, which may influence how fat they later become.

She said she and her colleagues will continue to follow the women and their babies to see whether giving probiotics during pregnancy has any influence on health outcomes in the children.

"The advantage of studying pregnant women to investigate the potential link between probiotics and obesity is that it allows us to see the effects not only in the women, but also in their children," she said. "Particularly during pregnancy, the impacts of obesity can be immense, with the effects seen both in the mother and the child. Bacteria are passed from mother to child through the birth canal, as well as through breast milk and research indicates that early nutrition may influence the risk of obesity later in life. There is growing evidence that this approach might open a new angle on the fight against obesity, either through prevention or treatment."

Latinen's study was funded by the Social Insurance Institution of Finland, the Academy of Finland and the Sigrid Juselius Foundation, a Finnish medical research charity.