Probiotics and the urologist

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Emerging from the stigma of once being referred to as "snake oil", excellent scientific and clinical evidence now exists to indicate that probiotics do indeed have a role to play in medicine. The proper definition of probiotics is important "Live microorganisms which when administered in adequate amounts confer a health benefit on the host", for several reasons. It rules out so-called probiotics that have no clinically proven, peer-reviewed data, and it states the need to have viable bacteria present, unlike these pseudo products which are often wrongly labeled, poorly manufactured, with low or no viability at time of use. Guidelines, prepared by the United Nations and World Health Organization are now available to guide physicians and consumers as to the types of strains with documented benefits. In urology, the most studied strains are Lactobacillus rhamnosus GR-1 and L. fermentum B-54 and RC-14. Their use daily in oral form, or once to three times weekly as a vaginal suppository, have been shown to reduce the urogenital pathogen load and the risk of urinary tract and vaginal infections. Organisms such as Oxalobacter formigenes, still in the R&D phase, offer great potential to reduce kidney stone formation via oxalate degradation in the intestine. Some studies using L. casei Shirota suggest a possible effect against bladder cancer, while studies using L. plantarum 299 show significantly reduced infection rates in patients undergoing major surgical procedures. In short, specific probiotic strains hold much promise for use in the urology setting.

Key Words: probiotics, urinary tract infection, bacterial vaginosis, surgical infection

Remembrance

Ernie Ramsey spent the last 2 years of his Residency Program in urology at Queens University in Kingston, after graduating from Queens University in Belfast. When Ernie came to Canada he already had inherent surgical skills, abundant energy and enthusiasm – all the ingredients for a special resident which, of course he proved to be. He rapidly acquired a reputation for clinical excellence and technical capability, and showed his abilities in residency organization and clinical research.

Our young staff and residents developed the program to provide ideal opportunities for learning – journal clubs were attended by all generally at our individual homes – lots of good article reviews, inevitably followed by urological gossip, and whenever possible the traditional ping-pong game. Said Awad and I steadfastly held on to the doubles title, much to Ernie's chagrin!!

Ernie presented two papers at his first Canadian Urological meeting in Ottawa and came away with two job offers – one with Ian Thomson in Missouri and one in Winnipeg – a difficult decision. I then watched Ernie's career develop and mature, and many

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times we have talked of those early days and of the subsequent cross roads that he faced. At the University of Manitoba he provided excellent teaching at both undergraduate and graduate levels, his surgical skills were widely appreciated and his continuing presentations and publications were both provocative and practical. He was particularly noted for his clinical trial work and contributions in prostatic diseases. He and Diane were a great team, and their friendship was treasured by many.

Ernie is sorely missed by all his many friends and colleagues and Margaret and I send our continuing sympathy to Diane and family.

Andrew W. Bruce

Introduction

The time has come for urologists, and indeed all physicians, to develop a clear understanding of the important role that the intestinal and urogenital microflora have on health and well-being. The application of exogenous bacteria to enhance the protective effects of these organisms, a concept termed "Probiotics", has now the scientific evidence to warrant clinical implementation on a number of fronts.

The term probiotics is defined " as live organisms which when administered in adequate amounts confer a healthy benefit to the host".[1] In 2002, a working group established under the auspices of the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO), established guide lines clearly defining what constitutes a true "probiotic".[2] These are:

- Identify and characterize the organism to genus and species using molecular typing
- Designate each specific strain, for example *Lactobacillus rhamnosus* GG
- Provide evidence of safety
- Provide efficacy data using an appropriate clinical trial design to show that the strain and product confer a health benefit on the host over and above any placebo effect
- Where appropriate, provide effectiveness data from human studies showing that the strain in product form is as good as or better than standard therapy for a particular condition
- Make appropriate health claims using data obtained with the strain/product in humans. Labels and complementary support material (brochures, web sites etc) must refer to the evidence for the strain/product

These important guidelines, once adopted by United Nations member countries, will provide a standard of excellence acceptable to physicians and other health professionals.

Although the concept of using "normal bacteria" to repopulate the gut flora has been around for many years, it was Nobel Laureate Elie Metchnicoff, in the early 20th century who raised its significance. Largely because of the success of antibiotic therapies, probiotic research and development was very limited until the past 5 years. Indeed, one of the major factors driving the current interest in probiotics is the ever increasing levels of bacterial resistance. This includes resistance of *E. coli* to fluoroquinolones and trimethoprim-sulfamethoxazole, two of the most commonly used agents in urologic practice.[3]

Physicians and surgeons have long been skeptical in their attitude to the value of probiotics, generally with good cause. Many products, currently available mostly through dietary supplement and direct marketing channels, are inadequately documented, have untested bacterial strains and too often contain contaminants or organisms not named on the label.[4] Too often the labeling shows viable count at time of manufacture, when the count at time of use is either non-existent or too low to confer a benefit. Techniques to enhance stability at room temperature and optimize passage through the acidic stomach and bile, are available but are too infrequently used in efforts to cut costs. In time, it can only be hoped that the FAO/WHO guidelines will be implemented and enforced, thus ensuring that all so-called probiotic products are indeed proven to confer a health benefit.

Of the few probiotic strains with good supporting clinical data and some understanding of their mode of action, most are targeted to gut health. The *Lactobacillus rhamnosis* GG strain (ConAgra, USA and Vallio, Finland) is the most documented followed by *L. rhamnosus* GR-1 and *L. fermentum* B-54 and RC-14. The GG strain has been shown in randomized, double-blind, placebo controlled studies to prevent and reduce the duration of diarrhea in children[5] and to prevent atopic dermatitis.[6] The oldest commercially available strain, *L. casei* Shirota (Yakult, Japan) has been marketed very successfully and over 9.5 billion units are sold annually in many countries (not North America) and some evidence suggests that in addition to immune modulation, the organism can reduce the recurrence of superficial bladder cancer.[7] Other well documented strains include *L. acidophilus* NCFM(Rhodia,USA) for lactose intolerance, and *L.reuteri* (Biogaia, Sweden) for diarrhea. Unfortunately, few physicians are aware of the proper

definition, guidelines and proven strains, and consumers or patients often do not appreciate the subtleties of this information and are sold on creative marketing stories. A survey of physicans in Nova Scotia in 2001 showed that 31% had no knowledge of probiotics.[8] Yet, a survey which we undertook over 10 years ago at the annual American Urological Association showed that 70% of urologists would be interested and willing to use a probiotic for prevention of urinary tract infection. The apparent lack of knowledge amongst general practitioners is not shared amongst well-educated female consumers, who represent the driving force behind the expanding natural remedy self-use market. Thus, the dilemma is how these consumers gain access to proven strains, and how physicians can be convinced of product effectiveness and how they can learn more about the field. A combination of enhanced industry standards, more good science and clinical trials, and quicker as well as more effective government legislation will improve the delivery of probiotics to a wider population.

Probiotics for women's health

Our group have pioneered basic, animal and human research in the development of lactobacilli probiotics for the restoration and maintenance of women's health, particularly the prevention of urogenital infections. Over 156 peer-reviewed manuscripts have been generated to identify, select and test the most appropriate strains for human use.[9,10] These studies have shown that lactobacilli can be inserted vaginally and orally to reduce the risk of yeast vaginitis, bacterial vaginosus (BV) and urinary tract infections (UTI).[11-17] Significantly, reduction in the incidence of recurrent UTI in women occurred using once weekly intravaginal capsules containing *L. rhamnosus* G-1 and *L. fermentum* B-54. Recently, a similar organism to B-54, namely RC-14 has been selected along with GR-1 for human use. These latter two organisms were selected specifically for their unique properties: GR-1 is inhibitory to Gram-ve pathogens and is resistant to spermicidal killing; RC-14 is effective against enterococci and produces a biosurfactant and proteins with marked anti-infective and apparent anti-flammatory activity.[18,19] These strains were obtained from the urethra (GR-1) and vagina (RC-14, B-54) of pre-menopausal women with no history of urogenital infection. Human studies have shown these organisms can effectively colonize both the colon and vagina when administered orally.[13,20] Recently, studies with *L.rhamnosus* GR-1 and *L. fermentum* RC-14, given by the oral route have shown improvement in the vaginal flora (in terms of reduced yeast and bacterial pathogens and increased lactobacilli) in healthy women as well as patients with asymptomatic bacterial vaginosis.[17] Possible modes of action include reduction in ascension of pathogens from the rectum/perineum to the vagina, modulation of the mucosal immune response and increased competition by lactobacilli.

Implications for probiotic implementation in urological practice

Non sexually transmitted uro-genital infections in women constitute a major health problem, and it is estimated that annually world wide one billion women suffer from UTI, BV and yeast vaginitis. Although all these disease entities respond to antimicrobial therapy, they have high recurrence rates. Furthermore, the adverse impact of many chemotherapeutic agents on the gut and vaginal flora is well known. In one study, a single course of broad spectrum antibiotic therapy for UTI led to the lactobacilli microflora of the vagina being significantly depleted or eradicated for up to 6 weeks.[21] As antibiotics do not alter the host's susceptibility to infection,[22] the dominant presence of pathogens in the vagina might explain the high recurrent infection rate or superinfection with yeast in many women.

Many patients are distressed by the physical discomfort, inconvenience and pain associated with bladder and/or vaginal infections, and often they become intolerant of the repeated courses of antinicrobial treatment required. Indeed, one study has shown that UTI has a significantly negative impact on the patient's quality of life.[23]

Probiotic therapy could provide a means to reduce recurrences and yeast vaginitis. In a small study of women given 3 days of antibiotics to treat UTI, there was a reduction in recurrences for patients given probiotics post-antibiotic treatment.[24]. This suggests there could be a dual role for probiotic therapy in women – to prevent recurrences after antibiotic use, and to maintain a normal vaginal flora. The latter raises the issue of 'what is normal'? This likely differs between children, pre and post-menopausal females. New molecular techniques are providing a better understanding and identification of the organisms within the vaginal vault and uncovering potential disease causing agents not before identified.[25-27] As far as is known at present, the absence of lactobacilli in women correlates with increased rates of infection, and thus the absence of these organisms is deemed to

represent an abnormal state. It appears that the vaginal microbial population fluctuates between a normal and abnormal state, such that at any given time, the majority of women may have an 'abnormal' flora. Clearly this does not always lead to symptomatic infections, but it does increase the risk of them occurring. The factors which cause an imbalance and progression to infection are the subject of several studies.

In another urological application, studies now suggest that calcium oxalate stone formation could potentially be prevented by the presence (naturally or exogenously applied as a probiotic) of *Oxalobacter formigenes*, an intestinal organism that essentially eats oxalates and stops their adsorption into the blood stream and emergence in the kidney.[28,29] A study showed that *O. formigenes* was present in 65% of 40 normal individuals and in 30% of 63 calcium oxalate stone formers.[30] The presence of the organism in recurrent stone formers was as low as 5.6% in stool. The extent to which probiotic ingestion can reverse the colonization and stone formation remains to be determined in humans, but animal studies provide some reasons for optimism.[31]

A broader place for probiotics in surgical management

In surgical management of patients, a protocol which suggests that bacteria be administered to improve recovery would be received by many as unconscionable. For many years, the practice of preparing patients for abdominal surgery has been to use broad spectrum antibiotic therapy to attempt to eradicate as many potential pathogens as possible. Yet, patients still die of infections and multi-drug resistant pathogens are plaguing the hospital system like never before.

In a radical departure from traditional practices, three randomized controlled trials were undertaken in seriously ill patients to determine if probiotic administration could reduce the incidence of infectious complications. These were carried out by administering *L. plantarum* 299 with fibre supplements to liver transplant recipients and patients undergoing abdominal surgery or with acute pancreatitis.[32-34] The results were surprisingly good and suggest a potential new paradigm for surgical patient management. In the liver transplant group, infection rates dropped from 48% to 13%, while in the abdominal surgery groups they fell from 30% to 10%. In terms of patient morbidity, mortality and healthcare costs, such reduction rates are very significant. Many mechanisms are being explored for this protection and they include modulation of immunity, stimulation of a protective gut mucus and tightening of cell permeability, reduced pathogen translocation, and competition between bacteria for nutrients.

Summary

While probiotics were vanquished as being too simple, and unnecessary 20 years ago, sufficient scientific and clinical evidence has been generated to show that they do indeed have a role to play in human health and well-being, including reduction in risk of disease. It may take some time for government regulatory agencies to allow such claims to be made on these safe natural products,[35] and it may take the pharmaceutical industry longer still to consider them as viable options to chemotherapies. For urologists in Canada at least, few clinically proven probiotics are available for patient use. If recommendations for patients to use products that follow the FAO/WHO Guidelines, the chances of some benefits being conferred should increase. Within the next 3 years, new products will become available, some as foods, others as dietary supplements or drugs. The case of VSL#3, an eight strain probiotic introduced recently for Crohn's and inflammatory bowel disease,[36] provides an example of how quickly the times are changing. □

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