Probiotics for the Developing World

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Abstract: Every minute of every day more and more children die of diarrheal diseases and women, and girls become infected by HIV. An estimated 7,000 women become infected each day. While many valiant efforts are being made to address these issues, until now they have proved to be markedly ineffective. The notion that lactic acid bacteria, formulated into food or dietary supplements, could have a role to play in slowing the morbidity and mortality associated with HIV/AIDS and gastroenteritis, is built upon sound clinical findings and scientific investigations, yet no international efforts have been placed in this approach, to date. We hereby summarize the reasons why such efforts should be made, provide an example of one model being set up in sub-Saharan Africa, and challenge the international community to consider the potential benefits of probiotics, especially for communities not reached by governmental and nongovernmental agencies.

Key Words: HIV/AIDS, developing world, probiotics, lactobacilli

(*J Clin Gastroenterol* 2005;39:485–488)

PROBLEMS IN THE DEVELOPING WORLD OF RELEVANCE TO PROBIOTICS AND PREBIOTICS

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" and prebiotics are "a non-digestible substance that provides a beneficial physiological effect on the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria."[1] The two major conditions responsible for morbidity and mortality in the developing world, which could potentially benefit from probiotic or prebiotic interventions, are diarrhea and HIV/AIDS. This review will examine the rationale for the introduction of probiotics into the developing world.

HIV/AIDS AND DIARRHEAL DISEASES

While advances in medicine and hygiene have increased the survival of children in their early life, one child still dies every 15 seconds from diarrheal disease, mostly associated with HIV/AIDS, or unsafe food and water. The American Academy of Microbiology Critical Issues Colloquia Program stated in 2002 that up to 60 billion cases of diarrhea occur each year[2] and these are a "scourge to humanity" and cost the United States alone up to $37 billion. This amounts to 50,000 cases every minute! Without question, practical on-site interventions are needed urgently to enable communities to enhance the health of their people in a self-sufficient and sustainable manner. Rotavirus is a significant cause of morbidity and mortality in children. In Peru, an estimated 1 in 1.6 children under 5 years of age will experience an episode of rotavirus diarrhea, 1 in 9.4 will seek medical care, 1 in 19.7 will require hospitalization, and 1 in 375 will die of the disease. In a country with only 0.4% of the world's population, there are around 384,000 cases, 64,000 clinic visits, 30,000 hospitalizations, 1,600 deaths, and an annual expenditure of U.S. $2.6 million just for children.[3]

PROBIOTIC INTERVENTIONS FOR GI DISEASES

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) published an Expert Panel Report in 2001[1] stating that "adequate scientific evidence exists to indicate that there is potential for the derivation of health benefits from consuming food containing probiotics." Furthermore, it stated: "The health benefits for which probiotics can be applied include conditions such as gastrointestinal infections, certain bowel disorders, allergy, and urogenital infections which afflict a large portion of the world's population."

As recommended by the WHO, clinical management of acute diarrhea must include replacement of fluid and electrolytes losses along with nutritional support.[4] Probiotic remedies often come as dairy drinks, and it is feasible that their use could constitute replacement of fluid and electrolyte loss, as well as provide anti-infective benefits. In a prevention trial performed in Peru, once daily intake of *L. rhamnosus* GG

Received for publication September 7, 2004; accepted December 15, 2004.
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6 days a week for 15 months in 204 undernourished children 6 to 24 months old, led to significantly fewer episodes of diarrhea (5.21 episodes diarrhea/child per year vs. 6.02 in placebo group; $P = .028$).[5] If this were to be translated to the Peruvian population alone, a 13% reduction in episodes would equate to approximately 50,000 fewer cases per year and a cost saving of at least $338,000 or at least $85 million worldwide (using conservative figures, treatment would be significantly more expensive in United States and other developed countries).

The latest estimates suggest that world wide, 2.5 million children die every year from 1 billion episodes of diarrhea.[6] The disease burden for all diarrheal diseases has been calculated to represent 76,340,000 working days lost per year, which again would have significance if there was 13% compound effect on parents who would otherwise have to care for sick children, 10 million working days would be saved. Such effects would be very significant for people trying to make a living in the developing world.

The potential impact is further supported by other studies, such as using *L. rhamnosus* GG strain along with *Bifidobacterium bifidum* and *L. reuteri* DSM 20016 to effectively treat acute bacterial and rotaviral diarrhea without adverse effects.[7–11] For example, in one randomized, placebo-controlled study of 40 patients between 6 and 36 months of age hospitalized with acute diarrhea, *L. reuteri* treatment ($10^{10–11}$ cfu) for up to 5 days resulted in reduction in duration of watery stools (1.6 vs. 2.9 in placebo) ($P = 0.07$).[12]

In India, the overuse of antibiotics and the inability of many children to receive proper nourishment, or adequate therapy for diarrhea has created a major health problem. Many families use fermented milk (curd or Dahi) as part of their daily diet, essentially subculturing the organisms themselves. There is some evidence that this can reduce the risk or improve recovery from diarrhea, but the effects appear to be heightened by addition of probiotic bacteria.[11,12] Indeed, one strain *L. casei* DN-114001, available in many parts of the world as Actimel, a milk-derived drink, has been reported to reduce diarrheal morbidity episodes by 40% in children tested in a 3-month follow-up.[12] While this suggests strongly that probiotic interventions have potential to benefit people in India, other factors have to be considered. First, the population prefers "local" solutions to health maintenance and restoration; therefore, it is unlikely that they would purchase on a regular basis a foreign company's milk product such as the one containing *L. casei* DN-114001. Second, the temperatures are extremely hot in India in summertime, reaching 48°C, and as most shops do not have air conditioning, the viability of probiotics becomes problematic. Very few companies have developed formulations able to retain high viable counts at 40°C to 48°C for periods of time that would allow suitable shelf storage from factory to consumer. The reason why probiotic products containing *Lactobacillus* GG and DSM 20016 are not yet sold in sub-Saharan Africa is unclear, but perhaps the companies do not feel there is sufficient profit or suitable distributors to justify sales. Sadly, it is in these regions that perhaps the greatest need for such products exists.

With a view to giving communities in Nigeria, Tanzania, and Kenya access to probiotics, *L. rhamnosus* GR-1 is being tested in various forms. This strain has now been successfully developed and clinically tested in Canada, in a yogurt form in which it retains suitable viability for 1 month. Staff and faculty at the University of Western Ontario and Lawson Institute, in collaboration with the Kenya Medical Research Institute, Kivilini Women's Group and Tanzanian personnel, have recently established a community kitchen in Mwanza. Local women are taught how to produce probiotic yogurt, and street owned cows and goats are able to provide a source of milk. This project allows people at the grass roots level to have access to probiotics which they could not otherwise obtain or afford. The model can be duplicated by other 'Western' and 'Northern' universities. The plight of children in India is so dire that 52% under the age of 5 are stunted, yet simple daily feeding with probiotics can reverse this.[11] Furthermore, a recent study of yogurt consumption in 202 subjects for 8 days has recently been shown to prevent antibiotic-associated diarrhea (12% vs. 24%; $P = 0.04$) and lead to significantly less total diarrheal days (23 vs. 60).[13] In our outreach, a training program will be established along with standard operating procedures (in appropriate languages), to allow the techniques to be set up effectively at each site. Ministry of Health officials will monitor production, quality control, and safety practices in each community. Various probiotic product formulations will be tested, including fermented milk, cheese, and yogurt. The concept is for the site to be self-sufficient within 2 years and for them to provide safe, beneficial products for their own and surrounding communities. In such translational studies, it is important to study socioeconomic and health outcomes and assess the impact of the local initiatives on the communities, including economy and quality of life. It is our view that such a scientific and clinically founded integrative approach, designed for the less well-served front-line communities involved in the HIV/AIDS fight, can provide significant benefits as well as teach all involved the advantages and limitations of probiotic regimens. This is what the FAO/WHO called for. If the international community, from businesses involved in probiotics to universities with student or fellow exchange programs, to philanthropic and aid agencies, could each undertake such outreach, one wonders how many lives could be saved or enhanced?

HIV/AIDS AND WOMEN

Globally, an estimated 7,000 women become infected each day. Sub-Saharan Africa is a region mired in poverty and hunger and now faced with rapid spread of HIV, especially among women and children. Over 67% of new HIV cases are in women, and 1 in 3 children entering the hospital has HIV. There are mounting pressures on societal infrastructure with over 13 million orphans, high HIV pregnancy rates, and teachers dying before they can impart suitable levels of education to the children. Over 0.5 billion women in Africa are at risk for HIV, and already in countries like South Africa 1 in 4 between 20 and 29 years is infected. The economic and social impact cannot be ignored with 45% pregnant women infected leading to children orphaned at a young age (currently 69,000 in Botswana), absenteeism and death in a workforce otherwise in its prime, leading to the fabric of society unraveling.

Factors contributing to heightened transmission among women and girls include lack of access to health information, lack of negotiation power over sexual encounters, rape by older males, dependence upon men for housing and income, diminished educational opportunities, low male use of condoms, and early age at first intercourse (12–14 years). Many problems account for the rapid spread of HIV (Figure 1), and these are not being adequately addressed by current interventional approaches, too many of which are geared to males not females, and too few of which reach the rural communities despite valiant efforts made by non-governmental agencies.

Methods to reduce the spread of HIV among sex workers, girls, and adult females have been markedly ineffective, mostly focused on condom use (of which too few are available, and women have little control over whether or not men will use them) and spermicides, long advocated but recently shown to actually increase the risk of infection by damaging the vaginal mucosa or inducing vaginal inflammation.[14] The first multimillion dollar vaccine trial failed miserably,[15] although high-tech efforts continue to develop an effective vaccine. The donation of anti-retrovirals is a good gesture, but it is far from sufficient to address the spread of the disease. Studies are required at the local level to examine what factors (gender, socioeconomic, cultural, political, etc) lead to alterations in lifestyle that impact well-being and risk of disease. The use of simple probiotic foods or dietary substances to potentially reduce the spread of HIV/AIDS needs to be foremost in the minds of people in positions of influence.

Potential Probiotic Effects for Women

Studies in Africa and Asia have shown that one major risk factor exists for HIV, gonorrhea, and *Chlamydia* acquisition in women, namely, the absence or depletion of lactobacilli in the vagina associated with an overgrowth of anaerobic pathogens causing bacterial vaginosis (BV).[16,17] The displacement of lactobacilli, for example, by *Gardnerella,* elevates vaginal pH and creates an environment within which the pathogens survive and can infect the host.[18] Black women are particularly susceptible to BV for reasons not yet understood and which are not related to socioeconomic status. The prevalence of BV globally ranges from 15% in otherwise healthy women in North America to 85% in various sex worker populations. In short, a strong case can be made that the absence of lactobacilli and dominance by various pathogenic organisms is not the preferred state for the host. The question is: can this state be altered in favor of health and reduced risk of HIV?

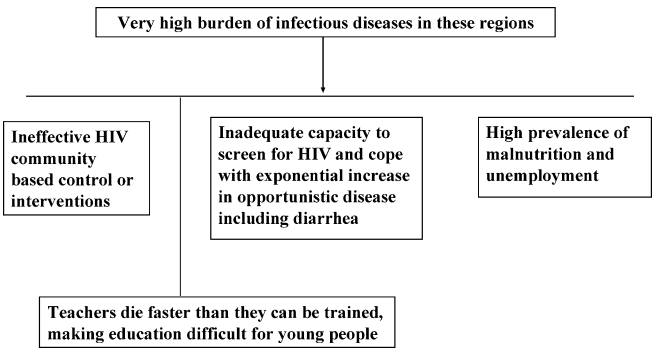

FIGURE 1. What is at the root of these problems?

Evidence is mounting that lactobacilli strains can kill viruses, colonize the vagina, and displace bacterial vaginosis pathogens known to increase the risk of HIV.[19,20] In a randomized, placebo-controlled study of 59 women, 8 cases of BV were reduced to 1 by daily oral use of capsules containing 10^9 *L. rhamnosus* GR-1 and *L. reuteri* (formerly *fermentum*) RC-14 compared with 7 cases unresolved by placebo.[21] Such lactobacilli safely administered by mouth,[22] may impart some benefits through mucosal immune modulation[23] as well as by ascending naturally from the rectal skin into the vagina.[24]

In terms of economic impact, an Italian study showed that the direct cost to care for an AIDS patient per year was up to Euro15,390,[25] making a global burden around U.S. $700 billion. If probiotic remedies only had an impact in 0.1% of this total, it would still represent a massive savings to overburdened healthcare systems.

According to one survey of 280 female university students in Nigeria, 55% perceived that they could acquire HIV within the next 3 years, and 82% stated they would welcome a probiotic for oral or vaginal use to enhance their health.[26] In the first studies of the strains in Africa, an animal model showed that they do not represent a safety risk,[27] while another showed that the appetite of pregnant mice was significantly improved with daily ingestion of strains GR-1 and RC-14, while the pups had a 30% mean weight gain and no cases of death.[27a] This provides support for human studies where nutrition in pregnancy plays a major role in the subsequent health and survival of the newborn. Further studies have shown that the vaginal microbiota of women in Nigeria is similar in *Lactobacillus* species to those of Canadian and European women (Anukam, manuscript in preparation), thus negating the argument that "Western" solutions cannot be applied to "African" problems.

Other exciting developments have been reported in which receptor sites for HIV have been imbedded into *Lactobacillus jensenii* with a view to them capturing the virus and preventing it from infecting the host.[28] While the first application is for vaginal protection against HIV, the potential exists to protect the rectum and also engineer lactobacilli to express receptors for other viruses such as herpes simplex virus.

In summary, probiotics represent a potentially significant addition to the armamentarium of interventions to prevent HIV in women and improve the quality of life of patients with AIDS. The mechanisms of action in ameliorating diarrhea are not fully known, and may involve multiple events including interference with pathogen adhesion, growth and toxin release, modulation of immunity, and manipulation of host factors that stop the diarrheal process.[29] In the case of vaginal probiotics, the mechanisms appear to include acidification of the environment, displacement of BV pathogens,[20] down-regulation of inflammation,[30] and killing of the virus.[19] Probiotic use, including for HIV/AIDS patients, appears to be safe[22,31] and is worthy of further testing to see if it has any role in HIV prevention in women. Strains such as *L. rhamnosus* GG,[5] *L. reuteri* DSM 20016,[10] *L. casei* DN114 001[12] and

Bifidobacterium lactis BB12[32] would be good choices for diarrheal treatment, and *L. rhamnosus* GR-1 for vaginal health.[33]

Key steps toward wider use of probiotics in developing countries include:

Funding of trials at the local level to assess applicability to different populations;

Introduction of proven products even if the price is not as high as would be obtained in the developed world;

Exchange of students to enhance training and eventually the development of new research centers focused on probiotic foods and supplements;

Publications and presentation of seminars or courses to introduce the concepts to healthcare professionals who likely are not aware of this field; and

Connecting with local industries, especially dairies, to provide advice and training on the creation and distribution of probiotic foods.

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