Introduction

“Live microorganisms which when administered in adequate amounts confer a health benefit on the host” (1) is a definition for probiotics proposed through the World Health Organization with implications that the microorganisms be specifically identified and benefits be scientifically defined and proven. The current reality is that the field of probiotics is an area of health care that is limited in terms of any broad-based regulations despite the significant commercial interests in this area for people to consume probiotics to improve “health,” prevent disease, or treat medical conditions. There are examples of specific probiotic strains being carefully identified and undergoing clinical trials. However, as a consequence of the lack of regulatory requirements for microbe characterization or efficacy trials many products currently available as “probiotics” through local health food stores, pharmacies or purchased through the Internet are lacking in these characteristics. In fact, mislabeling or contamination is documented for probiotic preparations (2–4). The most prevalent microorganisms used as probiotics are *Lactobacillus* and *Bifidobacterium* species. Other bacterial species including *Enterococcus*, *Streptococcus* and *Escherichia* are used (Table 1). As well, the fungus *Saccharomyces boulardii*, is also available as a probiotic. The potential and real benefits of probiotics have been reviewed in recent issues of *Practical Gastroenterology* (5,6). With the greater availability of health information for con-
Safety Issues of Probiotic Ingestion

PROBIOTICS: THE HOPE, THE HYPE, AND THE REALITY, SERIES #5

Table 1
Organisms used as probiotic agents

<table>
<thead>
<tr>
<th>Lactobacillus</th>
<th>Bifidobacterium</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. acidophilus</td>
<td>B. bifidum</td>
<td>Saccharomyces boulardii</td>
</tr>
<tr>
<td>L. casei</td>
<td>B. infantis</td>
<td>Bacillus cereus</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>B. breve</td>
<td>Bacillus subtilis</td>
</tr>
<tr>
<td>L. paracasei</td>
<td>B. adolescentis</td>
<td>Streptococcus thermophilus</td>
</tr>
<tr>
<td>L. plantarum</td>
<td>B. longum</td>
<td>E. coli</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>B. lactis</td>
<td>E. faecalis</td>
</tr>
<tr>
<td>L. lactis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. johnsonii</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. bulgaricus</td>
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</tr>
</tbody>
</table>

consumers, easier access of alternate health products not requiring a physician prescription, greater commercialization of probiotics and interest in direct health action by individuals, the use of food products or capsules with “probiotic” microorganisms is rising. Probiotics are advanced to consumers as “generally recognized as safe” natural products or food supplements without adverse effects on the basis that fermented foods have been ingested by humans for many years without clear harmful effects. It is only recently that microorganisms used as probiotics have been packaged in forms that allow for ingestion of high concentrations with encouragement to take these products for extended periods of time. There have been few safety studies but this review aims to update the primary care practitioner on the safety profile of probiotics and potential adverse effects of ingested probiotics.

SYSTEMIC AND DEEP TISSUE INFECTIONS

The most serious adverse event to probiotic administration is infection. *Lactobacilli* are found in approximately 0.1%–0.2% of positive blood cultures but sepsis or deep tissue infections resulting from ingestion of probiotics is thought to be rare (7,8). There are supportive retrospective analyses. In Finland, *L. rhamnosus* strain GG was introduced into dairy products in 1989. By 1999, annual consumption had increased considerably to an average 10^{11} colony forming units (CFU/person/year) (9). Finland required all positive blood isolates be recorded into a national database, allowing for a retrospective study of *Lactobacillus* sepsis in their population. Saxelin, et al (7) found that between 1989 and 1992, no infection was caused by the *L. rhamnosus* strain GG that was recently introduced as a dairy probiotic strain. When the database was examined for the years 1990–2000, Salminen, et al (9) found that of 48 confirmed cases of *Lactobacillus* sepsis, 11 isolates were identical to *L. rhamnosus* strain GG. There was no temporally increasing trend to associate the increase in strain GG intake with an increase in incidence of *L. rhamnosus* GG sepsis. Thus, the study indicated the greatly increased probiotic use had not led to an increase in *Lactobacillus* infections. As well, a recent meta-analysis of otherwise healthy children with acute gastroenteritis administered *Lactobacillus* did not reveal evidence of probiotic infections (10).

However, case reports exist in the literature of serious systemic infections with ingestion of probiotic bacteria. Representative examples of case reports include that of *L. rhamnosus* endocarditis and sepsis in a 67-year-old man with mitral valve regurgitation and carious teeth who chewed probiotic organisms. He presented with endocarditis after undergoing a dental procedure (11). Molecular analysis of the *Lactobacillus* strain isolated from his blood found it to be indistinguishable from the probiotic he had taken by mouth. In another report, a 75-year-old woman with a history of atrial fibrillation and stroke developed *L. paracasei* endocarditis. Molecular analysis showed the organisms responsible to be a *L. paracasei* strain also used in the fermentation process of dairy products (12). A 74-year-old woman with Type 2 diabetes mellitus with a liver abscess and pleuropulmonary infection caused by a *L. rhamnosus* molecularly similar to the probiotic strain GG has also been reported (13). This same strain has also been reported to cause infections in infants including an infant who developed sepsis in the post-operative period following repair of a double-outlet right ventricle and pulmonary stenosis and in a 6-year-old female with cerebral palsy and microcephaly (14). Both patients had central venous access in place and

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the authors discuss their concerns of gut translocation as responsible for the infection as compared to contamination of the central venous access devices (14).

Bifidobacteria are also commonly used as probiotics and are also used in the fermentation process of a wide range of dairy products. One study examined side effects and safety of two strains of B. longum in 39 healthy adults (15). It found no greater rate of adverse effects in the treatment group compared with placebo. Phagocytic activity of peripheral blood mononuclear cells was found to be higher in the placebo group for both opsonised and non-opsonised zymosan but whether this had any clinical relevance was not studied. Another study examined B. breve in 66 very low birth-weight (VLBW) infants and found no harmful effects (16). However, a case report of B. breve meningitis in an infant (not associated with probiotic administration) has been reported (17). This case highlights the concept that even presumed non-pathogenic organisms may cause infection in at-risk populations. One might expect future case reports of sepsis following ingestion of Bifidobacterium strains as the level of utilization of this probiotic approaches the level of use of Lactobacillus strains.

Saccharomyces boulardii is not normally found in humans but is a yeast fungus isolated from the lychee fruit and its properties of growing at 37°C and being intrinsically antibiotic-resistant have led to its use as a probiotic (reviewed in 5,6). This probiotic has been studied in different patient groups including those with antibiotic associated diarrhea without reports in these trials of fungemia (18,19). However, a case series of six critically ill adult patients with central venous lines who developed fungemia following administration of S. boulardii as a probiotic is published (20). In this series, there was an additional seventh patient in the same critical care unit as the others who developed Saccharomyces central line sepsis despite no oral administration of the probiotic (20). A review of other reported cases of Saccharomyces sepsis—including both children and adults using this form of probiotic—discusses this infection as an emerging disease (21). However, these patients were all very ill with reasons for this infection based either on increased gut translocation or central line contamination.

Taken together, the reports of probiotic infections raise such issues as the general need for care in the handling of powdered forms of probiotics, the need to know alternate forms of medical therapy patients may be self-prescribing and that patients should be made aware that there is a risk of infection with the ingestion of probiotics albeit seemingly quite small for otherwise healthy individuals without underlying medical conditions. While the otherwise healthy patient will have low gut translocation and an effective protective system in the body for removal of those organisms that do cross the barrier, patients that have artificial devices such as intravenous catheters, prosthetic or abnormal heart valves should be advised to use probiotics with caution.

MICROBE ISSUES: RESISTANCE, VIRULENCE TRANSFER AND VIABILITY

Some Lactobacillus species are known to contain chromosomal genes that encode for antibiotic resistance, particularly to vancomycin. Since vancomycin tends to be used as an antibiotic of last resort for bacteria with multiple resistances, this is a concern. Some of these species are commonly used in the food industry’s fermentation process. These can include L. casei, L. rhamnosus, L. curvatus, L. plantarum, L. coryneformis, L. brevis, and L. fermentum. However, studies have shown that chromosomally encoded vancomycin-resistance gene in Lactobacillus is non-transferable (22,23) in contrast to genes that are encoded on plasmids. This area of safety research is under current study.

Enterococcus strains are also used in the food industry as starter cultures for cheeses and yogurts and as probiotics. However, in contrast to Lactobacillus and Bifidobacterium strains, some Enterococcus strains are known to cause serious infections in humans and this problem is compounded as these strains are acquiring antibiotic resistance including that of vancomycin. Eaton and Glasson (24) found fewer virulence determinants in starter culture strains compared to food strains and fewer virulence determinants in food strains compared to medical isolate strains. Furthermore, acquisition of E. faecalis plasmid encoded virulence determinants including the possibility of antibiotic resistance occurred between starter strains and medical strains during their in vitro experiments. Whether virulence transfer can happen in the intestinal tract of humans is
currently hypothetical. Thus, the effect of ingesting a 10^{11} CFU/day of safe strain of *Enterococcus* for a person that may be carrying a nosocomial acquired medical strain with multiple virulence determinants is not known over the lifetime of the individual but there is opinion that the use of *Enterococci* as a probiotic should be used with caution (25).

Studies comparing efficacy of viable probiotic organisms compared to heat-killed organisms have suggested that the former have greater efficacy for both in vitro and clinical efficacy (26–29). This is a quality control issue that some producers and distributors are focusing on and is relevant not only from the consumer value perspective but heat-inactivated *L. rhamnosus* strain GG incorporated into a infant formula has been reported to be associated with adverse gastrointestinal symptoms and diarrhea as compared to an identical formula with the viable probiotic (30).

### SPECIAL POPULATIONS

#### Infants

Saavedra, et al (31) studied a formula containing *B. lactis* (strain Bb 12) and *Streptococcus thermophillus* in 131 healthy infants aged 6 months and older. For infant formula studies, growth is a primary determinant of safety and in their study there was no difference in growth between infants taking a formula with the two different probiotic bacteria and those infants on an identical formula that did not contain the probiotic microbes. Another recent study involved 201 healthy 4-10 month-old infants recruited from multiple day-care centers. They were fed formula with either *B. lactis* BB-12 or *L. reuteri* SD 2112 and investigators did not detect any differences when examining growth, behaviors or stooling compared to an identical formula without added probiotics (32). Similarly, there were no episodes of sepsis involving the probiotic bacteria administered for the probiotic-administered groups (21).

Colonization patterns are determined by the mode of parturition, the environment (i.e. neonatal units, home deliveries) and whether the child is breast-fed or bottle-fed (33). Among premature infants, the gut of the very low birth weight (VLBW) infant is colonized by less than three bacterial species at the 10th day of life and common enteric species *Bifidobacterium* and *Lactobacillus* could be found in only 5% of infants at one month of age (34). Studies have been undertaken with a hypothesis that replenishment of these organisms that are more likely to be found in breast-fed infants might reduce neonatal diseases. Dani, et al (35) administered 10^9 CFU/day to 295 VLBW infants and there were no *Lactobacilli* infections. Lin, et al (36) administered a strain of *L. acidophilus* and *B. infantis* to 180 VLBW infants after the seventh day of life. None of these infants had indwelling umbilical or venous access catheters. No episodes of sepsis from either *Lactobacillus* or *Bifidobacteria* were evidenced during the study. Infants younger than 3 months of age may be at risk of acidosis (see Intestinal disease) from ingesting high concentrations of D(–)-lactate producing probiotic organisms (37) although no formal evaluations have been undertaken.

### Intestinal Disease

Human metabolism produces the L(+)-isomer of lactic acid. If there is D(–)-lactate present in humans it would be as a consequence of bacterial metabolism of carbohydrates producing D(–)-lactate directly or indirectly from L(+)lactate through a DL-lactate racemase that some *Lactobacilli* species possess (38). Human cells metabolize and excrete D(–)-lactate poorly and should excessive build-up occur, acidosis will develop. Most patients reported to have this condition are those with short gut syndrome as occurs following mesenteric thrombosis, volvulus, or Crohn’s disease (39,40). Other types of patients developing this problem have included those that have undergone intestinal bypass surgery or patients with small bowel bacterial overgrowth (e.g. pseudo-obstruction) (39,40). One common feature among these patients is excessive carbohydrate exposure to D(–)-lactate producing bacteria. Development of this problem with excessive numbers of D(–)-lactate producing organisms colonizing the bowel is of concern as well. In fact, for those patients that develop this problem re-colonization with bacteria that are not D(–)-lactate producers have proven beneficial (41). Taken together, administration of D(–)-lactate producing probiotics should be carefully considered in patients at risk of developing D-lactic acidosis.
Immunocompromised Patients

There is precedent for their use in certain patient groups within this category of diseases. For instance, bacterial probiotics have been administered to patients with AIDS (42,43), cancer (44,45) and in the perioperative period of patients undergoing organ transplantation (44,46) without reports of development of infections due to the bacterial probiotics administered to them. It must be stressed that there are no studies to define the minimum patient parameters and immune parameters for the safe administration of bacterial probiotics to patients with their immune systems compromised on the basis of infections, disease states or medications used to treat underlying cancer. As discussed previously with the risk of infection, the use of yeast probiotics appears to be of considerable risk in ill patients in general with some of the adverse event case reports in post-transplantation, with HIV, on steroid therapy and in a child with leukemia (47–52). Yeast probiotic use should be questioned in these patients.

CONCLUSION

Over the past decade, consumption of probiotics has increased rapidly. It appears for most organisms used as probiotics that their ingestion into the human intestinal tract is safe. Patients that are very sick, those with chronic underlying diseases or those that have artificial implanted devices should be cautious in their use of probiotics, especially with using yeast probiotics. There are no consensus guidelines for safe parameters for the use of probiotics in immunocompromised patients and the use of probiotics in these patient groups would be best as part of ongoing studies. Greater regulations should be advocated to ensure quality control of products and efficacy. Some probiotics have certain proven benefits and specific strains should always be discussed much the same as specific antibiotics are discussed. At a minimum, the counseling of the small risk of infection should be undertaken with patients in much the same manner as patients are counseled for side effects of pharmaceutical agents requiring a prescription.
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