Safety concerns of Probiotic use: A review

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Abstract: Every day, millions of people consume probiotics for their perceived health benefits, but how safe are probiotics? Do probiotics cause invasive infection and if so, who is at risk? There is considerable interest in probiotics for a variety of medical conditions, and millions of people around the world consume probiotics daily for perceived health benefits. Lactobacilli, bifidobacteria, and lactococci have generally been regarded as safe. There are 3 theoretical concerns regarding the safety of probiotics: (a) the occurrence of disease, such as bacteremia or endocarditis; (b) toxic or metabolic effects on the gastrointestinal tract; and (c) the transfer of antibiotic resistance in the gastrointestinal flora. So, in order to deliver appropriate probiotic therapy both medical and dental practitioners should be aware of the adverse effects associated with probiotic use.

I. Introduction

Probiotics can be defined as “An oral supplement or a food product that contains a sufficient number of viable microorganisms to alter the microflora of the host & has the potential for beneficial health effects” (1, 2, 3). It can also be defined as “Live microorganisms that when administered in adequate amounts confer a health benefit on the host” (4). Most of the commercially available probiotics belong to the Lactobacillus & Bifidobacterium species, that are part of normal healthy gastrointestinal micro biota (5, 6, 7, 8).

Probiotic effects are strain specific, thus each individual bacterial strain must be tested separately for health benefit in question, and the effects described for one strain cannot be directly applied to others (9). Lactobacilli fall into the category of organisms classified as “generally regarded as safe” (10). Organisms that are regarded as safe along with lactobacilli, are lactococci, bifidobacterium and yeast. There are other probiotic organisms, such as enterococcus, bacillus, and other spore forming bacteria, as well as streptococci, that are not generally regarded as safe but have been used as probiotics. In this review, we will focus on the data regarding the safety of probiotics.

Risk factors associated with the use of Probiotics

The abilities of probiotics to survive and be metabolically active in the gastrointestinal (g.i) tract and to interact with the gastrointestinal mucosa and gastrointestinal microflora have led to 4 areas of concern about safety (11).

1. Potential for bacteria to translocate/transmigrate, crossing the g.i. barrier and resulting in invasive infection.
2. The possibility for some probiotic organisms to harbour resistance to antibiotics, leading to a potential for antibiotic resistance to be transferred from probiotic bacteria to other potentially pathogenic bacteria (12, 13).
3. Metabolic activity and immunologic effects of probiotics leading to possible deleterious metabolic effects and excessive immune stimulation (12, 14, 15, 16).
4. Finally we have concerns about product quality, since products that do not contain the probiotic on the label, or that contain contaminants may also place the consumer at risk.

Probiotics are generally considered safe when ingested orally or used vaginally and are well tolerated. One safety concern associated with probiotics is the potential for these organisms to cause systemic infections. Although rare, probiotic related bacteremia and fungemia have been reported (17). It is estimated that the risk of developing bacteremia from ingested Lactobacillus probiotics is less than 1 per 1million users (18), and the risk of developing fungemia from Saccharomyces boulardii is estimated at 1 per 5.6million users, and is estimated to be lower in healthy individuals (19).

Risk of bacterial translocation/transmigration

Translocation by intestinal bacteria is facilitated by numerous factors including intestinal mucosal injury, immunodeficiency, gut prematurity and abnormal bacterial flora (20, 21), as well as adherence of the bacteria to the mucosal surface (22). Risk factors for translocation have been studied in the mouse model. Zhou et al evaluated whether 3 probiotics, Lactobacillus rhamnousus HN001(DR20)TM, Lactobacillus acidophilus HN017 and Bifidobacterium lactis HN019(DR10) could translocate and cause invasive infection in an oral mouse model (23, 24). On the other hand, according to one study, there is no increase in the translocation of other bacteria when probiotics are given (25). In addition, probiotics mitigate the translocation of pathogens...
during their use (26). There is no evidence, from population based studies, of any increased risk of bacteremia or endocarditis due to probiotics (27).

**Table 1--**

Risk of transfer of antimicrobial resistance

The antibiotic resistance gene can be transferred by conjugation, transduction or transformation (29). At present, reports regarding the spread of antibiotic resistance among Lactic acid bacteria and Bifidobacteria suggest that resistant strains from human and animal colons are rather common, that confirms the transfer of resistances between commensal organism in the complex ecosystem of g.i.tract (30). There is a general concern that such microbes may harbour genes that may contribute to opportunistic infections (31).

Gastrointestinal toxicity studies

Due to potential impact of the use of probiotics on gastrointestinal physiology, there can be production of metabolites that are undesirable, especially in patients with short small bowel syndrome (32). There is a theoretical risk that the probiotic bacteria might lead to malabsorption due to de-conjugation of bile salts (33, 34). This might, therefore, increase the risk of colon cancer (34, 35).

Bacteremia and endocarditis potential

Organisms that have been associated with endocarditis or bacteremia includes L. rhamnosis, L. plantarum, L. casei, L. paracasei, L. salivarius, L. acidophilus and many other lactobacilli (34, 36). In addition to this, Lactococcus lactis and Leuconostoc species, as well as pediococcus species have been demonstrated to cause bacteremia and endocarditis (34). Bifidobacterium species have also been isolated from the blood and in patients with endocarditis (34, 37).

Risk of inadequate quality standards for Probiotics

Quality of probiotic products is a matter of great concern. Temmerman et al (38) studied 55 european products 30 dried food supplements and 25 dairy products. No viable strains could be isolated from 11 (37%) of the dried food supplements, 15 either had more probiotic species isolated than were listed on the product label or contained species not listed on the product label. In only 4 (13%), did the probiotic product label match the contents.

Safety of S.boulardii as probiotic

Since the 1950s, S.boulardii has been used internationally & extensively as a probiotic (39). Studies of S.boulardii in populations other than the healthy general public have demonstrated its efficacy for reducing recurrence of Clostridium difficle infection (CDI) when used in combination with standard therapy. A multicenter, double blind, placebo controlled trial investigated the effects of S.boulardii (1g/day) for 4 weeks in combination with vancomycin (high dose 2g/day or low dose 500mg/day) or metronidazole (1g/day) to patients with either initial or recurrent CDI (34, 40). Recurrence rates were 16.7% for patients receiving S.boulardii with high dose vancomycin compared with 50% for patients receiving high dose vancomycin & placebo (p=0.04) (34, 40).

Safety of Lactobacillus rhamnosis GG

Over a period of time, it has been administered to children with chronic inflammatory disease, including crohn’s disease and juvenile rheumatoid arthritis, to adults with inflammatory bowel disease, and to patients with HIV infection (41). Till date, no significant adverse events have been demonstrated in these and other controlled trials (42). Factors ensuring the safety of lactobacillus GG, includes absence of plasmids, good enzyme profile as it elaborates beta-glucuronidase and urease, and it also secretes an antimicrobial agent (43, 44). In conclusion, lactobacillus GG has been proven safe both invitro and invivo, as well as in a number of human studies (42, 45). Although there have been rare cases of bacteremia and liver abscess in patients with short gut syndrome, overall, it is a safe probiotic.

Genetically engineered probiotics

Genetic modification of probiotics has been undertaken to increase certain physiologic or immunologic properties within the organism and to use the probiotic as a mucosal delivery system or a vaccine vector (17,43). Their use is limited.
Steps to monitor safety of probiotics

To monitor the safety of probiotics as they are introduced and increasingly used around the world, it is important to conduct population based surveillance for the isolation of probiotic bacteria from patients with infection. There should be knowledge of the susceptibility profile for any strain used in clinical trials (17, 46, 47).

Significance of probiotic safety in dentistry

Probiotics are widely used in dentistry mainly in prevention of dental caries, periodontal diseases, halitosis (48, 49, 50, 51). Till date only few studies were reported in relation to safety of probiotics in the field of dentistry. Mackay et al (52) reported the development of L. rhamnosus endocarditis (strain not specified) after a dental extraction in a 67 year old man with mitral regurgitation who was taking probiotic capsules daily. More studies in this discipline can contribute towards probiotic safety issues in dentistry.

II. Conclusion

Overall probiotic use is safe in most of the cases. However, probiotic use should be avoided in patients having abnormal gastrointestinal mucosal barrier, children having short gut syndrome, immunocompromised patients, patients with central venous catheters, we also conclude that there is risk of plasmid mediated transfer of antibiotic resistance in some probiotic strains. Careful risk assessment for patients and proper handling of the probiotic during administration need to be conducted before using probiotics as drugs in institutional setting. Vigilant reporting of adverse events resulting from probiotic use is necessary to establish the safety profile of these agents when they are used in other than healthy populations.

Why this paper is important to paediatric dentists

This review highlights the safety concerns of probiotics in detail. Probiotics are used very frequently by the dentists especially pediatric dentists for the prevention of dental caries. So it is of utmost importance for the pediatric dentists to know about the risk factors associated with probiotic use and this review puts more light on this particular aspect of probiotic use.

References

[16]. A.A. Salyers, A. Gupta et al., "Human intestinal bacteria as

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Table 1. Clinical cases in which lactic acid bacteria or bifidobacteria have been isolated (28)

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Endocarditis</th>
<th>Bacteremia</th>
<th>Other infection</th>
<th>Total</th>
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<tbody>
<tr>
<td>Lactobacillus</td>
<td>7</td>
<td>8</td>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>L. acidophilus</td>
<td>3</td>
<td>3</td>
<td>2</td>
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<td>L. casei</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>L. plantarum</td>
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<td>2</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>19</td>
<td>5</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Leuconostoc</td>
<td>2</td>
<td>23</td>
<td>8</td>
<td>33</td>
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<tr>
<td>Pediococcus</td>
<td>-</td>
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<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>61</td>
<td>40</td>
<td>155</td>
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Table 2. CONCERNS RELATED TO ORAL HEALTH (53, 54)

<table>
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<th>Research Needed</th>
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<td>Natural existence in oral cavity</td>
<td>Screening the oral micoflora</td>
</tr>
<tr>
<td>Colonization in the mouth</td>
<td>Microbiological &amp; chemical studies</td>
</tr>
<tr>
<td>Effect on biofilm &amp; resistant flora</td>
<td>In vitro &amp; in Vivo studies</td>
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<tr>
<td>Effect on mucosal integrity</td>
<td>In vitro &amp; in Vivo studies</td>
</tr>
<tr>
<td>Age dependent colonization</td>
<td>Microbiological studies</td>
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<tr>
<td>Role in dental caries</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td>Best way of installation</td>
<td>Randomized controlled trails</td>
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<tr>
<td>Synergistic combination of strains</td>
<td>In vitro &amp; in vivo randomized controlled trails.</td>
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