Review Article

An Updated Overview on Safety of Probiotics

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ABSTRACT

It is claimed that medical remedies have been dangerous since the age of Hippocrates. Cyril Chantler has rightly stated that "Medicine used to be simple ineffective and relatively safe. Now it is complex effective and potentially dangerous". This reflects the risk and benefits of modern drugs. There is low risk with modest benefit offered by most probiotics. There are health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Probiotics are sometimes named as "pharmabiotics" because now days their manufacture and production have increased many folds and pharmaceutical industries are earning dollars and dollars. The sales of probiotics have gained an immense height in present pharma market. Thus Probiotic use in clinical medicine has increased tremendously. But the safety of probiotics in humans receiving nutritional support has to be understood completely. There are always chances of potential hazards of probiotic bacteria for immunodeficient patients. There is an urgent need to evaluate deficiencies in labeling of commercial probiotics. The compatibility of probiotics with cow's milk has to be established. It is to be emphasized that various probiotics differs in respect of bioavailability, biological activity, doses and composition.so proper implementation of pharmacovigilance programmes can dramatically help to increase safety standards of probiotics.

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INTRODUCTION

"Probiotics" mean "for life" and are defined as "Live microorganisms" which when administered in adequate amounts confer a health benefit on the host [1]. This definition excludes bioactive polysaccharides nucleotides and proteins [2]. At present probiotics also includes yeast (*Saccharomyces cervisiae*) and various species of bacteria namely- Lactobacillus Streptococcus Enterococcus Bifidobacterium Propionibacterium Bacillus and Escherichia.

There are important caveats regarding probiotic safety that needs emphasis. Firstly the safety record of probiotic strains in current use does not necessarily apply to new strains in development. Second probiotic strains are highly varied without a uniform mechanism of action. Third there is no such thing as zero risk as far as probiotics are concerned. Fourth there is poor public understanding of risk / benefit analysis which needs to be addressed. Fifth the quality of product in terms of potential contaminants may be more important. Finally although probiotics have microbiota and generally regarded as safe the relationship between commensals and pathogens is not one of mutual opposites but rather they are at different positions on a spectrum of low to high pathogenic potential.

WHEN FRIENDLY BACTERIA BEHAVE ABNORMALLY

Probiotics are consumed as a supplement to harness the commensal microbiota. The distinction between commensals and pathogens becomes critical. Organisms with a propensity to cross mucosal barrier are obviously pathogens. But the distinction from commensals is not always evident when the host has an acquired barrier

defect or a genetic susceptibility. It is quite difficult for the host to distinguish pathogens from commensals or consumed probiotics because the patterns involved in the recognition of pathogens are also expressed by non-pathogens including probiotics [3].

For some commensals there is production of symbiosis-associated molecular patterns. This is demonstrated by Bacteroides fragilis which produces an immuno-modulatory polysaccharide that signals through Toll-like receptor 2 on regulatory T-cells within the host to suppress TH -17 effectors and thus inhibit adverse immune response [4].

The host has a back-up surveillance system for the detection of danger signals from the microbiota and for modifying the composition of the microenviroment. This is done by inflammasomes which are intracellular multi-protein complexes that sense exogenous and endogenous stress. Experimental defects in inflammasome function have shown their importance within the epithelium and mucosal phagocytes not only detecting pathogenic components within the microbiota but also in initiating a cascade of immunologic responses to restore compositional equilibrium within the microbiota [5 6].

Depending on the host susceptibility some organisms behave either as a commensal or as a pathogen. The example of commensals in the wrong place at the wrong time is that of the baby born prematurely and before full development of immunity. Here colonization with commensals poses a threat. The use of probiotics in premature infants is still controversial [7-9].

Another example of risk to benefit is illustrated by Helicobacter pylori which depend on the bacterial strain including the age and susceptibility of host [10]. The organism is acquired during childhood but after a variable period of apparent health causes peptic ulceration in adulthood. At the later age the organism may cause gastric cancer. The potential benefit from the same organism also depends on the age of host. In early life H pylori may protect against asthma and infections but later it protects against reflux associated complications such as metaplasia and neoplasia at the gastroesophageal junction.

DESIGNER TURBO PROBIOTICS

Genetically engineered organisms may comply with the current definition of a probiotic and are likely to be viewed as pharmaceuticals from a regulatory perspective. Safety issues involve the recombinant product engineered for production by the organism. Public health concerns regarding the containment of the genetically altered strain from the wider environment after excretion need attention. Insertion of the therapeutic transgene into the bacterial thy A locus which codes for thymidylate synthase makes the organism dependent on thymine or thymidine in the local microenviroment thereby limiting its viability after excretion. If the engineered organism reacquires the A gene the transgene is eliminated from the bacterial genome. The safety and efficacy of this strategy has been explored experimentally with the food-grade organism lactobacillus lactis engineered to express interleukin-10 trefoil factor and anti-tumour necrosis factor nanobodies [11-13].

Another approach has been to use an anaerobic commensal bacteroides ovatus engineered to produce either keratinocyte growth factor or transforming growth factor-beta under the control of dietary xylan with efficacy in experimental inflammatory bowel disease [14,15].

ADVERSE OUTCOMES WITH PROBIOTICS

Probiotics and Necrotizing enterocolitis:

It is now well documented that use of probiotics in pre-term infants reduce all-cause mortality rate and prevents occurrence of necrotizing enetrocolitis in pre-term nenonates [16].

PROBIOTICS AND PANCREATITIS

In PROPATRIA study [17] probiotic consumption resulted in higher-than-expected mortality rate in patients receiving a probiotic preparation. The increased mortality in the probiotic limb was attributed to bowel ischaemia. Thus this raises sufficient concern with the use of certain types of probiotics in acutely ill patients.

PROBIOTICS AND OBESITY

A possible link between probiotics use and obesity is based on circumstantial evidence that use of probiotics as growth promoters in the farming industry [18]. Probiotic are

actually used to promote lean body mass [19-20]. A comparative meta-analysis of different lactobacillus species on weight gain in humans and animals claimed that different lactobacillus species vary in their apparent effects on weight change which are host specific [21]. However a study by Delzenne [20] found no causal link between obesity and probiotics.

PROBIOTICS AND SEPTICAEMIA

A study by Ohishi [22] found that postoperative probiotic therapy in neonate with omphalocoele resulted in bifidobacterium septicaemia.

PROBIOTIC AND ANTIBIOTIC RESISTANCE

The potential transfer of antibiotic resistance from fed probiotics to the commensal microbiota in vivo is an important ongoing concern and reflects the importance of whole-genome sequencing of candidate probiotic strains. Antibiotic resistance remains a valid concern with enterococci than with lactobacilli and bifidobacteria [23-24]. A high degree of genetic stability has been associated with lactobacillus and bifidobacterium strains used in commercial probiotics.

SAFETY RECORD OF PROBIOTICS

The overall consensus on safety is relative. Various cases of sepsis proven to be linked with lactobacilli and bifidobacteria have been rarely reported [22-25]. Such organisms transmigrate across the mucosal barrier less readily than other commensals but this feature may not apply to all probiotics particularly those from different genera [20-25]. It must be emphasized that most experience with probiotics has been with lactobacilli and bifidobacteria but the safety record with enterococci non-lactobacillus and non-bifidobacterial strains are sparse and needs to be verified [26]. Although concerns have been expressed about risk of probiotics in immuno-suppressed patients but the record to date is encouraging [27-29]. But still there is need for continual vigilance for unanticipated adverse effects.

ACCURATE LABELLING OF PROBIOTICS: AN URGENT NEED

Safety assessment of probiotics should also include microbials contaminants. There are also concerns regarding inaccurate labeling. Health–food outlets contain probiotic with charming attractive labels with dramatic false claims of curing various diseases so consumers and buyers should not get trapped in such attractive labels but they should exercise their own discretion. It is well documented that several retail probiotic products have been found to contain microbes that were not mentioned on labels [30-32]. This circumstance is more likely to be caused by dubious quality control. There are always an ample chances for potential microbial contamination in the production process and this signals the importance of choosing a reputable supplier. Potential hazards also include the risk of allergies to milk and other allergens in probiotics which need specification on the label [33].

CONCLUSION

Probiotics have a long record of safety but still zero risk does not exist. Pharmaco-vigilance is required for unexpected adverse effects particularly with birth of designer turbo probiotics. As probiotics use becomes more wide-spread there are always the chances of antibiotic resistance due to emerging new bacterial strains. In this respect it is important to acknowledge that the distinction between a commensal or probiotic and a pathogen is a matter of debate. Quality control of probiotics may be more important than assessment of the properties of the probiotic constituent itself.

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