WILL PROBIOTICS BE BANNED FOR THE SEVERELY IMMUNOCOMPROMISED?

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According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) definition, probiotics are live microorganisms, which when administered in adequate amount confer a health benefit on the host. The Polish Society for Probiotics and Prebiotics is strongly advocating this definition and the safety aspects that FAO/WHO stress.

The fact that many beneficial microorganisms have a long history of safe use in a large population and are generally considered as safe, as well as that most studies do not show any adverse events related to probiotics may have been shaken by some recently available data, primarily owing to the publicity related to PROPATRIA (PRObiotics in PAncreatitis TRIAl) study in the Netherlands. The statement released by the International Scientific Association for Probiotics and Prebiotics following the results of this Dutch study lists some very important conclusions, questions some aspects of study and calls to the scientific community to use the term probiotic only if appropriate criteria are met, but probably one single point from these conclusions will be vital for future clinical trials on probiotics, i.e. establishment of safety of the approach when treating vulnerable patients, especially research to define proper animal models of safety. The table below lists some recent studies described in the literature and their outcomes:

Table 1. Recently published studies on microbes with clinical applications and their unexpected outcomes.

Published study	Patient groups	Condition	Strains & doses	Results	Conclusions
Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial *Lancet* 2008;371:651-9.	Probiotics group n=152 and placebo group n=144	acute pancreatitis	Ecologic 641 (*Lactobacillus acidophilus, L. casei, L. salivarius, Lactococcus lactis, Bifidobacterium bifidum, and B. lactis*). Total daily dose of 10^{10} bacteria given via nasojejunal tube.	Infectious complications: 46 in probiotics group vs. 41 control (none by administered strains). Bowel ischaemia: 9 in probiotics group vs. 0 control. Deaths: 24 in probiotics group vs. 9 control.	Speculated mechanism of bowel ischaemia: increased local oxygen demand to already critically reduced blood flow or local inflammation at the mucosal level? "...probiotic prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Probiotic prophylaxis should therefore not be administered in this category of patients."
Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of *Lactobacillus* GG supplementation *Pediatrics* 2008;121:e850-6.	Probiotics group n=50 and placebo group n=44	atopic dermatitis	*Lactobacillus* GG (American Type Culture Collection 53103). $5x10^9$ colony-forming units twice daily *per os*.	Atopic dermatitis: 14 in probiotic group vs. 12 control (comparable severity). Recurrent episodes of wheezing bronchitis: 13 in probiotics group vs. 4 control.	"Supplementation with *Lactobacillus* GG during pregnancy and early infancy neither reduced the incidence of atopic dermatitis nor altered the severity of atopic dermatitis in affected children but was associated with an increased rate of recurrent episodes of wheezing bronchitis. Therefore, *Lactobacillus* GG cannot be generally recommended for primary prevention."
Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial *J Allergy Clin Immunol* 2007; 119:184-91.	Probiotics group n=89 and placebo group n=89	atopic dermatitis	*Lactobacillus acidophilus* LAVRI-A1. $3x10^9$ L. acidophilus LAVRI-A1 daily *per os*.	Atopic dermatitis: 23 in probiotic group vs. 20 control (comparable severity). At 12 months, the rate of sensitization was significantly higher in the probiotic group ($p = 0.030$).	"Early probiotic supplementation with *L. acidophilus* did not reduce the risk of AD in high-risk infants and was associated with increased allergen sensitization in infants receiving supplements. The long-term significance of the increased rate of sensitization needs to be investigated in further studies. These findings challenge the role of probiotics in allergy prevention."

Discussion: There are documented situations in the literature when the use of microbial products has resulted in unexpected outcomes, contrary to what the authors have actually hypothesized. There are also reports in the literature of infections caused by genera that are usually considered beneficial. Moreover, only little is known about the immunological mechanisms of action of probiotics and their effects are probably strain-specific. Experts agree that probiotics are used on a very large scale and basically show no adverse events, but looking further, not many probiotic strains have documented randomized, double blind, placebo-controlled trials on large populations showing their safety in special situations, e.g. in chronically ill or severely immunocompromised subjects. The studies described show different dosages as well as modes of administration, that may play a role in the hypothetical "overdosing" of the bacteria and have an indirect influence on adverse events (and not being the isolated agent of infection).

Conclusions: Does the future hold any more surprises and will we see labels on probiotics stating: „ATTENTION! Not to be used in the severely ill or immunocompromised"? Can probiotic use show any adverse events at all? And will we see the origin of a somewhat controversial, rare condition, namely "probiotic infection"?

Two action items that we should definitely consider in the near future that will improve safety, are:

- Investigation and definition of proper animal safety models, that will enable
- Performance of safety trials on defined animal models, before investigating probiotics in a preferably large, multicentre, double-blind randomized placebo-controlled trial settings.

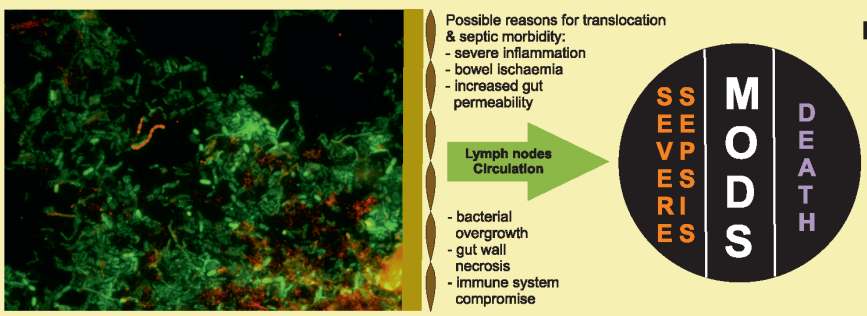

Figure 1. Probable pathway from gut through sepsis to multiple organ dysfunction syndrome and death.

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