

Discussion Group 2

Probiotic acute and long term safety: where do we stand in 2022?

Dan Merenstein, chair and Mary Ellen Sanders, co-chair

Thursday, June 16. 8:30 -13:00

Background

Commonly marketed probiotics are often presumed to be safe. Ten years ago, [a large review published by the RAND Corporation](#) found 11,977 publications, of which 622 studies were reviewed. In 235 studies, only nonspecific safety statements were made (“well tolerated”); the remaining 387 studies reported the presence or absence of specific adverse events. The review concluded, “The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence.” However, RCTs do not represent the totality of evidence on probiotic safety. There have been large cohort studies without serious adverse events reported. Further, global consumption of probiotics (dominated by *Lactobacillaceae* and *Bifidobacterium* probiotics), estimated at about \$40 billion USD retail sales in 2017, suggests that large amounts of common probiotics are being consumed without safety issues.

However, theoretical and proven adverse events from probiotic consumption exist and probiotic safety has recently come under attack in several high profile publications ([here](#), [here](#) and [here](#)). Furthermore, probiotics without a history of safe use or qualified presumption of safety (QPS) status are under development. These ‘next-generation’ probiotics raise additional concerns.

Therefore, further examination of probiotic safety is warranted. **Our objectives will be to examine both acute and long-term potential risks and give some guidance on what studies should report.** Probiotic safety encompasses properties inherent to the probiotic, to the consumer/patient, and to how the product is manufactured ([contaminated probiotics products represent a safety concern](#)). Issues such as target population (e.g., age, clinical condition), mode of administration (e.g., oral, naso-jejunal), and exposure (dose) are all relevant factors to this discussion.

Figure 1 from [Rouanet et al. 2020](#) provides a useful summary of safety considerations.

Note: Safety of probiotics has been addressed previously in 2 ISAPP discussion groups. The outcome of one is published [here](#); the other was not published. Also, a USP expert panel published on quality, purity, quantification and identity issues important in probiotic manufacturing ([here](#)).

Outline

Moderator – Colin Hill

Each talk should be ≤ 10 min to allow time for discussion

1. Introduction (Dan Merenstein) 8:30 - 8:45
2. Are there additional **acute adverse events, beyond what is required by good clinical study practice**, which should be monitored in human probiotic trials? It is agreed that all trials should follow [CONSORT](#) adverse event reporting practices. However, are there additional acute safety monitoring that are specific to probiotics? For example, [bacteremia](#), fungemia, adhesion, antibiotic resistance gene transmission, antibiotic resistance gene enrichment, D-lactate production, aberrant immune stimulation, microbiome alteration? Or are there probiotic-specific concerns for certain age groups (e.g., neonates) or clinical conditions (e.g., short bowel, critically ill, immunocompromised)? Are there specific considerations for safety of next-generation probiotics? Is the decision tree published by [Pariza et al. 2015](#) sufficient for considering safety issues for next-generation probiotics or are there other issues that specifically need to be addressed? **8:45-10:45**
 - a) Are there population groups (age, disease/health status, etc) where extra monitoring is indicated or where additional safety studies should be considered? (Maria Carmen Collado)
 - b) Is there evidence that antibiotic resistance genes are transferred from a probiotic to the resident microbiota? (Lorenzo Morelli)
 - c) Increased antibiotic resistance genes among resident microbiota. (Niv Zmora)
 - d) Delayed microbiota recovery. (Niv Zmora)
3. Safety issues associated with products as marketed **10:45-11:15**
 - a) Introduction about concerns. (Andi Shane)
 - b) Manufacturing issues related to probiotic quality, purity, and identity. (Greg Leyer)

Break **11:15-11:30**

4. Are there **long-term adverse events** from probiotic administration that should be monitored? **11:30-12:45**
 - a) What type of microbiome assessment (how long, what is tracked) is currently expected for microbiome-altering drugs/biologics (antibiotics, metformin, PPIs, etc)? Is the thinking on this changing?
 - b) What standards should probiotics be held to? To what extent does isolation from human commensal microbiota inform safety for a next-generation probiotic? (Bruno Pot)
 - c) Should potential long term microbiome alteration disqualify a strain for use by certain populations? (e.g., preterm infants or children)? (Geoffrey Preidis)
 - d) Most current probiotics do not colonize. If a probiotic does colonize, is it a concern? (Colin Hill)
5. Summary/conclusions/next steps 12:45-13:00 pm
6. Compile summary slides to present next day (Dan, Colin, Mary Ellen and others who want to help) **Over lunch and/or 5:30-6:00 pm**