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EDITORIAL

Probiotics and synbiotics reduce infective complications from colorectal surgery

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Recent advances in the prevention of infective complications from colorectal surgery have largely centred on the evolution of bowel preparation to include selective decontamination of the gut through the introduction of oral broad-spectrum antibiotics. Much of this theory is based on a combination of surgical dogma, retrospective data [1], and experimental evidence that suggests bacteria maybe causally associated with anastomotic breakdown through the production of collagenase enzymatic functions [2]. However, selective decontamination assumes that gut bacteria play no role in the recovery from surgical injury or oncological outcomes, either by optimising wound healing or by ensuring the optimal efficacy of adjuvant chemotherapeutic strategies [3]. More problematically, this strategy promotes antibiotic resistance.

The gut microbiome describes the entire habitat of the intestine, including all microbes, their genomes, and surrounding environmental conditions [4]. This is not only highly individualised and niche specific, but microbes are essential for the maintenance of gut homeostasis. Through its regulation of the innate immune response, the microbiome plays an important role in determining the systemic response to surgical injury and it also maintains the health of the intestinal barrier preventing translocation of commensal organisms into the systemic compartment and, ultimately, sepsis.

Symbiotic commensal bacteria are thus critical mediators of anastomotic healing, and in this new systems model of surgical wound healing, the pathogenicity of microbes is not just determined by the state of tissue perfusion, but also by the stresses that 'surgical exposome' places upon them [5]. Thus, novel bowel preparation approaches that promote mucosal microbial diversity and the symbiotic functions of the gut microbiome may be of specific benefit to the patient recovering from colorectal surgery. A 'probiotic' is defined as a "live microorganism that, when administered in adequate amounts, confers a health benefit on the host". The probiotic definition is important, because it states that these bacteria must be alive when they reach the gut, they have to be there in enough numbers to do the job, and the mechanism by which they improve our health must be known [6]. A 'synbiotic', also contains a prebiotic fibre, which is a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits upon host health.

In this context, the findings by Chen et al. are therefore of importance [7]. The authors present a comprehensive meta-analysis of 1566 patients taken from 14 RCTs of probiotic and synbiotic therapies for the prevention of infective complications during colorectal surgery. They report a 37% reduction in post-operative infection risk across all studies, and this benefit remained (18% reduction) after accounting for any publication bias. This observation is in keeping with previous meta-analyses in this field [8], and conceptually, it is also in keeping with animal models of anastomotic healing where probiotics have been found to be of benefit [9]. Of particular interest, patient benefit was seen across several categories of post-operative wound infection, including septicaemia, wound infection, central line infection, pneumonia infection, urinary infection, and incidence of diarrhoea. However, it should be noted it is not clear from these studies what the specific infecting organisms were.

The meta-analysis of probiotic trials in surgery is fraught with challenges. In this review, the majority of trials were arguably underpowered for the primary endpoint and three were not blinded. Indeed, Chen et al. report a positive publication bias. Ten of these studies used varying strains of bacteria (predominantly from the Lactobacillus or Bifidobacteria genus) and yeasts (e.g., *Saccharomyces boulardii*)

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within their probiotic interventions making a direct comparison challenging, while four used a probiotic and prebiotic combined (synbiotic). These fibres consisted of inulin, pectin, starch, fruco, and oligo-saccharides which are all likely to have different therapeutic mechanisms and dose responses. Neither the doses of the prebiotics nor the probiotics are reported in this analysis. The subgroup difference between probiotics and synbiotics was not significant ($p = 0.54$); however, it is impossible to say from this data if this is robust given the small prebiotic patient numbers and intervention heterogeneity.

Moreover, the duration of pre-operative dosing varied greatly which is challenging in colorectal cancer surgery where it may not be possible to adequately engraft the probiotic into the gut during prehabilitation phase. Of the 14 trials reviewed, five dosed pre-operatively (2–8 day range), 8 used both pre and post-operatively, and one used them post-operatively (0–15 day range). Subgroup analysis showed that pre-operative administration was beneficial in reducing the risk of developing post-operative infectious complications, which is intuitive, but this still does not provide compelling evidence that could be turned into practical guidance by clinicians wishing to use this therapy. Perhaps most problematically, all of the studies in this analysis reported using antibiotics, and again, there was variance in both pre- and post-operative dosing strategies and antibiotic class. Finally, none of these studies reported on safety data or complications from probiotic usage, although, in general, these are considered food stuffs and they are safe.

One of the greatest challenges for surgical probiotic RCTs is that none report on a probiotic mechanism or test a mechanistic hypothesis. Indeed, very few objectively assess a dose response, e.g., through a stool quantification analysis, that demonstrates the probiotic has even reached and engrafted within the intended target organ. Moreover, none determine the impact on the broader microbiome taxonomy or its functions. This is critical if a causal demonstration between probiotic or prebiotic function and complication risk reduction is to be demonstrated, as per the definition of probiotics and prebiotics provided by the International association for probiotics and prebiotics [6].

This is not an easy task, however, as microbiome functions are influenced by patient factors and almost all aspects of a surgical intervention, including enhanced recovery protocols, nutritional strategies, pharmacology or neoadjuvant therapy, cancer stage, faecal diversion, the local hospital microbiome, and the operative route (minimal vs. open surgery). None of these things are reported consistently in the trials analysed here. Moreover, perturbations in microbiome functions have been casually associated with multiple oncological and inflammatory conditions of the gut, and many patients coming to surgery have an 'abnormal' microbiome structure or function, exacerbated by cachexia or illness. If probiotics are going to be adopted into clinical practice, it is important that we not only provide evidence for these confounding variables on their safety and efficacy, but that we are able to define the specific mechanisms through which they have benefit.

Probiotic technologies are rapidly advancing towards synthetically engineered 'live biotherapeutics'. These next generation probiotics are a class of organisms developed exclusively for pharmaceutical application, that can be targeted towards host immunology or pathogenic drivers of clinical relevance [10]. Therefore, it is now feasible that the microbiome can be selectively targeted for patient benefit and improved surgical outcomes. The data presented by Chen et al. suggest that well-powered, robust probiotic trials should now be prioritised as a legitimate strategy for improving the safety of colorectal surgery by optimising surgical gut health rather than through the destruction of its biodiversity.

Declarations

Conflict of interest James Kinross has received speaker fees from Yakult and sits on an advisory board for Ysopia Bioscience.

Ethical and informed consent Not applicable.

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