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## Letters

### Probiotics: sorting the evidence from the myths

Shimonti Chatterjee and John Fraser  
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To the Editor: We read Pham and colleagues' recent article<sup>1</sup> with interest, as evidence mounts against the use of probiotics in critically ill patients. Although a plausible and attractive theory, probiotics in the patient with acute illness now appear ineffective, if not positively harmful.

A recent randomised trial of probiotics in 298 patients with severe acute pancreatitis showed a non-significant rise in infective complications,<sup>2</sup> in keeping with results of previous studies of critically ill patients.<sup>3,4</sup> Disturbingly, mortality in the probiotic group was more than double that in the placebo group ( $P < 0.01$ ). Bowel ischaemia was a prominent feature of deaths in the probiotic group (eight patients), but was not associated with any deaths in the placebo group ( $P < 0.004$ ). It may be that non-occlusive mesenteric ischaemia in critical illness is exacerbated by the added bacterial load itself, or through a pro-inflammatory response by gut epithelial cells.

While probiotics may be a benign and beneficial adjunct to enteral feeding in certain clinical situations, there is persuasive evidence that probiotic therapy is associated with increased infective complications in critically ill patients and significant mortality in patients with severe acute pancreatitis. Until there is evidence to the contrary, we believe probiotics should not be administered to patients with severe acute illness.

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Sanjaya N Senanayake

To the Editor: Pham and colleagues commented on the effects of probiotics; however, not much is known about the impact of probiotics on weight gain and obesity. It is known that a predominance of certain bacteria, such as *Lactobacillus*, in the bowel can promote weight gain. Many of these bacteria are found in probiotic products.

The human intestinal microbiota is predominantly colonised by the Firmicutes and Bacteroidetes phyla of bacteria. *Lactobacillus* and *Bifidobacterium*, found in a number of probiotic products, belong to the Firmicutes phylum. A study has shown that obese people carry a higher proportion of bacteria from the Firmicutes phylum and that there is a statistically significant decrease in the proportion of Firmicutes bacteria as they lose weight.<sup>3</sup> A similar pattern of Firmicutes predominance has been found in obese mice. Furthermore, the microbiota of the obese mice were more likely than those of lean mice to break down otherwise indigestible polysaccharides from the diet.<sup>4</sup> In other words, a higher proportion of Firmicutes bacteria was associated with increased and more efficient caloric uptake from food.

These data did not necessarily imply causation, so the investigators performed another experiment. They transferred intestinal microbiota from obese and lean donor mice to germ-free mice, and found that the mice who received microbiota from the obese donors had a significant increase in body fat after 2 weeks compared with the recipients from the lean donors.<sup>4</sup> It is therefore likely that the bacteria often found in probiotics can cause weight gain.

Obesity in children and adults is a major health problem in developed nations. Given the increasing use of probiotic products in such countries, large studies should be performed to

characterise the association between probiotics and obesity. Such studies may not find any association or may find that there is only a dose-related risk. If there is an association, probiotics may still prove useful in certain circumstances (eg, for weight gain in children failing to thrive).

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Mimi Pham, Daniel A Lemberg and Andrew S Day

*In reply:* The comments by Chatterjee and Fraser regarding the danger of administering probiotics to patients with acute severe illnesses are important additions to the debate on the risks and benefits of probiotic administration. We also thank Senanayake for his interesting comments on the possible role of probiotics in weight gain.

The recently published multicentre trial<sup>1</sup> describing unexpected adverse events associated with probiotics in acutely unwell patients with severe pancreatitis is one example of an adverse outcome following probiotic administration. The use of probiotics in patients with severe comorbidities and in those who are immunocompromised is also contraindicated. There are reported cases of *Lactobacillus* GG sepsis in premature babies with short gut syndrome,<sup>2</sup> and *Saccharomyces boulardii* fungaemia has been described in immunocompromised patients.<sup>3</sup>

It is interesting to note that two systematic reviews have assessed the efficacy of probiotics in prevention of necrotising enterocolitis in premature (< 33 weeks' gestation) and very low birthweight (< 1500 g) infants.<sup>4,5</sup> Both reviews concluded that probiotics may decrease the incidence of necrotising enterocolitis in preterm infants, and that severe adverse events were not associated with probiotics in these unwell and immunodeficient patients. However, there were insufficient data to comment definitively on the short-term or long-term safety of probiotics in these infants; this will require assessment in future large trials.

The increased scrutiny of probiotics resulting from the publication of the adverse outcomes in adults with severe acute pancreatitis<sup>1</sup> may, by necessity, slow the commencement and progression of these larger trials in infants in the neonatal intensive care setting.

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