

University of Groningen

Probiotic prophylaxis in predicted severe acute pancreatitis - Reply

Besselink, Marc G.; van Santvoort, Hjalmar C.; Buskens, Erik; Akkermans, Louis M.; Gooszen, Hein G.; Dutch Acute Pancreatitis Study Grp

Published in:
LANCET

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Besselink, M. G., van Santvoort, H. C., Buskens, E., Akkermans, L. M., Gooszen, H. G., & Dutch Acute Pancreatitis Study Grp (2008). Probiotic prophylaxis in predicted severe acute pancreatitis - Reply. LANCET, 372(9633), 114-114.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

On the basis of all of the above points, one cannot conclude that probiotics in general present a risk in enteral feeding.

I declare that I have no conflict of interest.

Philippe Marteau
philippe.marteau@lrp.aphp.fr

AP-HP, Medico-surgical Department of Digestive Diseases, Lariboisière Hospital, 2 rue Ambroise Paré 75010 Paris, France

- 1 Besselink MGH, van Santvoort HC, Buskens E, et al, for the Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **371**: 651–59.
- 2 van Minnen LP, Timmerman HM, Lutgendorff F, et al. Modification of intestinal flora with multispecies probiotics reduces bacterial translocation and improves clinical course in a rat model of acute pancreatitis. *Surgery* 2007; **141**: 470–80.
- 3 Marteau P, Shanahan F. Basic aspects and pharmacology of probiotics: an overview of pharmacokinetics, mechanisms of action and side-effects. *Best Pract Res Clin Gastroenterol* 2003; **17**: 725–40.
- 4 Alfaleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev* 2008; **1**: CD005496.

Authors' reply

Gregor Reid and colleagues correctly cite the definition of a probiotic provided by the Food and Agriculture Organization and WHO: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host". This does not mean that if such a product shows negative effects in a new study in a different population, the product should no longer qualify as a probiotic. From now on we will refer to the product used as a "combination of probiotic strains" or "the combination" because the individual strains have shown beneficial effects in previous studies.

Contrary to Reid and colleagues' suggestion, our combination was designed after rigorous selection studies.¹ In several animal studies and smaller clinical studies, no negative effects of the combination were detected. As a consequence, we feel that it was probably not the combination but the administration of the combination together with the severity of the disease that was

largely responsible for the effects obtained.

The implication that the increased mortality rate in the probiotics group was caused by a higher rate of organ failure on the day of randomisation in the study product group is incorrect. None of the baseline characteristics differed significantly between the groups. Furthermore, in a post-hoc subgroup analysis, having excluded patients with organ failure on the day of randomisation, mortality was still twice as high and bowel ischaemia was significantly more frequent in the group receiving the study product.

Bala Reddy and John MacFie propose "hypercaloric feeding" as a potential cause of bowel ischaemia. This was a post-hoc, quite heterogeneous, endpoint and whether it was initiated by organ failure, inflammation, or other unknown factors is unclear. It is, however, unlikely that it was related to hypercaloric feeding as such, because the feeding regimen—jejunal infusion of multifibre nutrition—was identical in both groups and the administration of the study product, with a negligible caloric load, was the only difference.

Philippe Marteau raises concerns about the dose of probiotics, and we agree that studies on doses are indeed lacking. However, several trials, in patients with acute pancreatitis and patients scheduled for elective abdominal surgery, have used even higher doses of probiotics with a similar route of intrajejunal (bolus) administration.^{2–4}

As for our alleged conclusion that probiotics in general present a risk in enteral feeding, we feel that this does not accurately reflect our cautious interpretation that probiotics can no longer be considered harmless under all conditions, especially in critically ill patients.

We declare that we have no conflict of interest.

Marc G Besselink,
Hjalmar C van Santvoort,
Erik Buskens, Louis M Akkermans,
*Hein G Gooszen, on behalf of the
Dutch Acute Pancreatitis Study Group
h.gooszen@umcutrecht.nl

University Medical Center Utrecht, PO Box 85500, HP G04.228, 3508 GA Utrecht, Netherlands (MGB, HCvS, LMA, HGG); and University Medical Center Groningen, Groningen, Netherlands (EB)

- 1 Timmerman HM, Niers LE, Ridwan BU, et al. Design of a multispecies probiotic mixture to prevent infectious complications in critically ill patients. *Clin Nutr* 2007; **26**: 450–59.
- 2 Rayes N, Seehofer D, Theruvath T, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation—a randomized, double-blind trial. *Am J Transplant* 2005; **5**: 125–30.
- 3 Rayes N, Seehofer D, Theruvath T, et al. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. *Ann Surg* 2007; **246**: 36–41.
- 4 Olah A, Belagyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg* 2002; **89**: 1103–07.

According to Marc Besselink and colleagues, the increase in mortality in patients with pancreatitis treated with probiotics was due to bowel ischaemia.¹

It has been suggested that most small-bowel diseases have a common final pathogenic pathway.² Accordingly, enterocytic damage by various assaults (biochemical, immunological, microbiological, vascular, etc) leads to an increase in intestinal permeability. This increased permeability results in a tissue reaction as luminal substances gain access to the mucosa where bacteria are the main neutrophil chemoattractant.²

The prototype of this damage is enteropathy caused by non-steroidal anti-inflammatory drugs,³ but there are more than 30 situations in human beings in which an increase in intestinal permeability leads to a uniformly prevalent and severe enteropathy.² These enteropathies cannot easily be distinguished from each other, even by enteroscopy or histologically (on which the changes resemble ischaemia). The inflammation can respond to antimicrobials (metronidazole), implicating resident commensal anaerobic bacteria in the pathogenesis.⁴

The patients described by Besselink and colleagues had pancreatitis, and