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Letter to the Editor

Influence of Prophylactic Probiotics and Selective Decontamination on Bacterial Translocation in Patients Undergoing Pancreatic Surgery: A Randomized Controlled Trial. *Shock* 35:9–16, 2011.

To the Editor: We read with interest the paper by Dr. Diepenhorst et al. (1) entitled "Influence of prophylactic Probiotics and Selective Decontamination On Bacterial Translocation in Patients Undergoing Pancreatic Surgery: A Randomized Controlled Trial." However, we are troubled by the clinical conclusions the authors draw from their small laboratory-based mechanistic study.

We are surprised at the low sample size of 30 patients. Expecting a 20% difference in bacterial counts between the group means is optimistic, as is 15% difference in SD, which undoubtedly resulted in the remarkably low numbers needed in this study. Also being satisfied with 80% statistical power is not a very demanding threshold. A 90% statistical power and a 5% SD would require sample size of around 260. This would perhaps have given the conclusions of this study a little more credibility. With only 10 patients in each group, we would suggest not much can be concluded.

Much is made in the discussion of the potential importance of probiotics. However, we interpret the animal data, which the authors cite as suggesting selective decontamination of the digestive tract (SDD) to be superior. Furthermore, the authors refer to a German randomized controlled trial (RCT) in liver transplant recipients (2), which demonstrated probiotics to be significantly better than SDD. However, half of the infections in this study were due to enterococci and coagulase-negative staphylococci causing pneumonia and cholangitis in the patients receiving SDD. Pneumonia due to these low-level pathogens is rare, and if excluded from the analysis, then probiotics would not appear to be of such benefit.

The same researchers published their first RCT assessing the efficacy of probiotics in acute severe pancreatitis 3 years ago (3). In 298 patients, there was increased mortality in patients with severe pancreatitis given probiotic prophylaxis (16%) compared with placebo (6%). The researchers found that prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. They concluded that probiotic prophylaxis should not be given in severe pancreatitis, although at that time the evidence for bacterial translocation in this disease was overwhelming (4). The researchers confirmed this crucial pathogenetic pathway using clinical end points in their placebo-controlled group (5). In 141 patients with pancreatitis, they concluded organ failure and mortality were all associated with intestinal barrier dysfunction early in the course of acute pancreatitis. The contrasting views on translocation between the two RCTs from the Dutch Acute Pancreatitis Study Group are difficult to reconcile (6).

We agree with the authors who caution against drawing any conclusions from their study with only 10 patients per group. We feel that absolutely no comment can be made about intestinal permeability, bacterial translocation, or more importantly the use of probiotics. If the intention of the authors was to show superiority of probiotics over SDD, we believe the design of their RCT was ill conceived both in terms of end point and subset of patient group selected.

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Reply: We thank Petros and colleagues for their comments on our recent article. With reference to the points they have raised, we have the following comments.

We would like to emphasize that our randomized controlled study was designed to explore the mechanistic immunological background of bacterial translocation and local inflammatory responses. As stated in the article, the study was not aimed toward a clinical evaluation and hence not powered to evaluate clinical outcomes. Accordingly, the study design was not targeted at demonstration of superiority of either treatment, as suggested in our final comment.

We agree with the sample size calculation the authors provide. However, we would like to point out that our explicit aim was to power this study for a mechanistic end point. In light of this mechanistic background, we believe that our sample size calculation with a threshold of 80% power is acceptable and in accordance with the Consolidated Standards of Reporting Trials (CONSORT) criteria. Furthermore, we have used a highly sensitive multiplex ligation-dependent probe amplification technique complementary to quantitative polymerase chain reaction, as well as unique baseline lymph node samples to explore the mechanism of bacterial translocation. Using these sensitive techniques, we detected bacteria in some of the baseline lymph nodes. Measurements in lymph nodes did not demonstrate the induction of inflammatory mediator expression during surgery or an increase in bacterial DNA. Contrary to the authors' statement, using these sophisticated techniques, we can indeed comment on the mechanistic background of intestinal permeability, bacterial translocation, and the use of probiotics based on these measurements.

The authors suggest a difference in viewpoint on bacterial translocation between our study and the earlier randomized controlled trials in patients with acute pancreatitis from the Dutch Pancreatitis Study Group (1, 2). We assume the authors refer to the association found between probiotics and bacterial translocation in the PROPATRIA study, whereas there was no association between bacterial translocation and probiotics in the current study. Alongside the earlier mentioned differences in end points between both studies, our study is performed in patients after major abdominal surgery, whereas the PROPATRIA trial was performed in patients with predicted severe acute pancreatitis. Essential differences in levels of organ failure and intestinal hypoperfusion can be expected in these patient categories. Taking into account these differences, the unifying hypothesis as suggested in our study may remain in which bacterial translocation functions as a promoter of septic morbidity instead of an initiator. According to this theory, bacterial translocation after abdominal surgery is part of a normal antigen-sampling process in the gut. However, when bacterial translocation overwhelms the host's immune defenses or the immune response is otherwise defective, septic complications may arise. In concordance, patients with acute pancreatitis in the aforementioned randomized controlled trial treated with probiotics showed an increase in bacterial translocation when organ failure was present, whereas patients without organ failure showed a decrease in bacterial translocation (2).

It is not entirely clear what the authors refer to with their statement that the animal studies cited in the discussion suggest a superiority of selective decontamination of the digestive tract (SDD). The cited studies by Seehofer (3) and van Minnen (4) both demonstrate a reduction in bacterial translocation in animals treated with probiotics in models of simultaneous liver resection and colonic anastomosis and acute pancreatitis without including SDD as a treatment group. Hence, in our view, these studies do not support a superiority of SDD.

Finally, we would not support excluding pneumonia on grounds of the identified pathogens being an unlikely cause of this complication, as suggested by the authors. We believe the study by Rayes and colleagues (5) is a well-designed prospective, randomized, placebo-controlled trial in which there are insufficient arguments to exclude a relevant complication group from the analysis.

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