Cytokine responses to lipopolysaccharide in vivo and ex vivo : Genetic polymorphisms and inter-individual variation

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CHAPTER 3

Letter to the Editor

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E.F. Schippers, J.T. van Dissel, No effect of preoperative selective gut decontamination on endotoxemia and cytokine activation during cardiopulmonary bypass: a randomized, placebo-controlled study, Critical Care Medicine, 31(1):334-5, Copyright (2006), with permission from Lippincott Williams & Wilkins.

To the Editor:

We read with interest the comment by Dr. Oudemans-van Straaten and colleagues (1) on our trial investigating the effect of preoperative selective gut decontamination (SGD) on endotoxemia and cytokine activation during cardiopulmonary bypass (2). Their main point of criticism concerns the choice of neomycin over tobramycin in our SGD regimen. Furthermore, they claim that there is a lack of correlation between fecal aerobic Gram-negative bacilli and endotoxin concentration. Dr. Oudemans-van Straaten and colleagues (1) suggest that the use of neomycin instead of tobramycin is responsible for the absence of an effect of our SGD regimen on endotoxemia. We would like to counter their critical notes.

The SGD regimen used in our randomized controlled trail was highly effective in eradicating aerobic Gram-negative bacilli (AGNB) from the bowel; 73% of the patients taking the trial medication had no AGNB at all, whereas others had strongly reduced numbers in the culture of a rectal swab (2), confirming previous studies on the effectiveness of this regimen in hematology and bone marrow transplant patients (3;4). This finding implicates that the regimen has a very potent antimicrobial activity and thereby reputes the theoretical objection made by Dr. Oudemans-van Straaten and colleagues (1) that neomycin is "inactivated" by feces (1). Moreover, their proposition is based on rather artificial experiments that showed inactivation of several antibiotics by fecal material *in vitro*. These findings remain of undetermined significance since they have never been shown to correlate with the ability of the selected antibiotics to reduce AGNB or endotoxin in feces (5). Furthermore, the neomycin dose used in our study (250 mg every 6 hrs, i.e., 1000 mg/day) is very high. Even in the theoretical situation that <99% of the total amount of neomycin would be "inactivated" by feces, the remaining free concentration would still be well above the "minimal inhibitory concentration" of most target microorganisms (e.g., fecal amount is approximately 200 g/day, total concentration of neomycin is about 5000 µg/g feces, 1% of this equals about 50 µg free neomycin/g feces). Their remark that neomycin, as opposed to tobramycin, fails to show "anti-endotoxin" properties is not substantiated by the literature they refer to: In the study by Rogers et al. (6), neomycin was combined with streptomycin and amfotericin B and not with polymyxin as we did, making direct comparison impossible. The suggestion of Dr. Oudemans-van Straaten and colleagues(1) that tobramycin has strong "anti-endotoxin" properties is not substantiated by the study of Sjolin et al. (7), which showed no such property of tobramycin when added to cefuroxime-treated *Escherichia coli* cultures. The effect of aminoglycosiden in lowering endotoxin concentrations, although they might have a slightly different antibacterial spectrum, is most likely due to their mode of action being

rapid killing and inhibition of endotoxin synthesis and not an “anti-endotoxin” effect as such (8). Altogether we do not find it feasible to attribute “anti-endotoxin” properties to antibiotics as a separate entity apart from their primary mode of action being antimicrobial activity. Polymyxin is not an exception to this rule; the mode of action of this unique bactericidal polypeptide is binding to the bacterial outer membrane components, mainly being lipopolysaccharides and phospholipids. Not surprisingly, this compound is able to neutralize much of the toxic actions of endotoxin, that is, mainly *ex vivo* (9;10).

We do not believe that endotoxin and AGNB levels do not correlate. Several studies have shown this correlation (6;11;12).

We have no doubt that the SGD regime used in our study, like other studies showing correlation between reduction in AGNB and endotoxin concentrations, lowered fecal endotoxin concentrations. Therefore, our conclusion remains that reducing AGNB in the gut from patients undergoing elective cardiac surgery does not reduce the perioperative endotoxemia and subsequent inflammatory response. These findings suggest that, at least in humans, the total size of the free endotoxin pool is not the key limiting factor in the pathophysiological mechanism that controls circulating endotoxin during cardiac surgery (2). For instance, the lower endotoxin content due to Gram-negatives other than the AGNB could well account for a concentration of endotoxin that already saturates the underlying translocating mechanism in a reperfusing bowel.

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