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Antibiotic Prophylaxis in Severe Acute Pancreatitis: Do We Need More Meta-Analytic Studies?

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Several guidelines on acute pancreatitis suggest that carbapenems should be used prophylactically and should be continued for 14 days, and that the development of infected necrosis should be assessed using fine-needle aspiration and the sample should be cultured for germ isolation and characterization [1]. In routine clinical practice, antibiotics are used to cure both extrapancreatic infections which appear during the course of acute pancreatitis and infected pancreatic necrosis and also as a prophylaxis in those patients who have pancreatic necrosis in order to prevent possible infection from the necrosis. In the treatment of extrapancreatic infections, the most used antibiotics were cephalosporins whereas carbapenems, glycopeptides and antifungal antibiotics were the most used antibiotics in the treatment of proven infected pancreatic necrosis [2]. Moreover, there are very few topics in pancreatology which cause as much debate as that regarding the utility of antibiotic prophylaxis in severe acute pancreatitis. There are very few human randomized studies and there are more meta-analyses published than studies published. Of course, the cost of a meta-analysis is much less than carrying out a study on the efficacy of antibiotics in severe acute pancreatitis. Thus, I would like to discuss the latest meta-analytic study coming from the United States [3]. In brief, the authors carried out a systematic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, using PubMed, Google Scholar, and Ovid as search engines without language restriction until the end of May 2008. They screened 367 articles of which 55 were found to be relevant to pancreatitis and antibiotics; of these latter 55 articles, only eight met the inclusion criteria: randomized controlled studies; severe acute pancreatitis diagnosed with contrast-enhanced computed tomography and any of the severity criteria such as Acute Physiology And Chronic Health Evaluation II (APACHE II), Imrie classification and increased C-reactive protein levels greater than 120 mg/L; necrosis evaluated by contrast-enhanced computed tomography; prophylactic antibiotics administered intravenously; defined length of antibiotic treatment, and morbidity and mortality measured objectively. Sensitivity analysis was applied to the results to determine heterogeneity among the studies. The authors pooled 502 patients from 8 studies [4, 5, 6, 7, 8, 9, 10, 11]. The majority of the patients (56%) had alcoholic pancreatitis, followed by biliary pancreatitis (24%) and pancreatitis due to other causes (20%). The age of these patients ranged from 43 to 59 years and the length of hospital stay ranged from 18 to 95 days. There were 253 patients with severe acute pancreatitis who received prophylactic antibiotics, and 249 patients were randomized to the placebo arm. Overall, there was no protective effect of antibiotic treatment with respect to mortality. With respect to morbidity, antibiotic prophylaxis did not protect against infected necrosis or surgical intervention. There was, however, an apparent benefit as regards non-pancreatic infections, with a relative risk reduction of 40%, absolute risk reduction of 15%, and number needed to treat of 7. Some comments are necessary; first of all, there was heterogeneity in the studies considered and only 5 studies [5, 6, 8, 10, 11] were considered to be of high quality according to the Jadad *et al*. scale [12]. Thus, very few studies were available for a meta-analytic study. Regarding the antibiotics used as prophylaxis, only half of the studies used carbapenems [4, 5, 8, 11], other studies used cefuroxime [6] ofloxacin [7] and ciprofloxacin [10, 11], associated or not with metronidazole, and the last one, published in abstract form only, used meropenem

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or ciprofloxacin plus metronidazole [9]. This is a crucial point, because the differences in the ability of the various antibiotics to penetrate into necrotic pancreatic tissue are well known. In fact, the choice of antibiotics in preventing infected necrosis during necrotizing pancreatitis should be based on their antimicrobial activity, penetration rate, persistence and therapeutic concentrations in the necrotic pancreatic area; these requisites are provided by pefloxacin and metronidazole and, to a variable extent, by imipenem and mezlocillin [13]. Finally, two studies considered in the meta-analysis [10, 11] did not reach the number of patients required by the calculated sample size. One study was stopped after an adaptive interim analysis [10] and, as pointed out by the authors themselves, the sample size was not large enough to detect potential beneficial effects of low magnitude or potential benefits involving infrequent secondary end points such as mortality, pancreatic necrosis, shock, and renal insufficiency; a second study [11] was stopped due to restriction of resources for continuing the trial.

It is also important to note that an apparent benefit was found in the meta-analysis regarding the development of non-pancreatic infections. In a recent multicenter study from the Dutch Acute Pancreatitis Study Group [14], it was found that the mortality rate was higher in patients with pneumonia, bacteremia, infected necrosis and pancreatic necrosis when patients with each specific infection were compared to all other patients in the study. As it is now clear that half of relevant infections occur in the first few days of acute pancreatitis, prophylactic strategies should be initiated immediately after admission and randomized controlled trials of antibiotic prophylaxis, commencing treatment in the first 72-120 h after onset of symptoms [10, 11], need to be repeated with a much earlier start of prophylaxis. In fact, results from a recent randomized trial, showing a significant reduction in 'extrapancreatic sepsis' by starting antibiotic prophylaxis on admission to hospital, support this hypothesis [15].

As pointed out by the authors themselves of the meta-analyses published to date [3], other limitations of the studies considered in the meta-analysis were inherent in the primary study design such as inclusion criteria, duration and dosing of antibiotics, assessment of severity of disease, nutritional support, and resuscitative measures, the relatively small number of patients in each individual study, and different outcome measurements. In addition, the inclusion of non-blinded studies limits the findings because these patients should have received surgical intervention when investigators realized that they were not receiving antibiotics. In conclusion, we do not need more meta-analytic studies on this topic; on the contrary, additional and well-carried out studies are required to explore the benefits of antibiotic prophylaxis in severe acute pancreatitis, also taking into account the adverse effects, the effects of the varying duration of the therapy, and whether the outcome of the infection is related to the etiology.

Conflict of interest The author has no potential conflicts of interest

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