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Antibiotic Prophylaxis in Acute Necrotizing Pancreatitis: Yes or No?

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The risk of complications and death in necrotizing pancreatitis is dependent on the intensity of proteolytic insult and on variable biological responses, also comprising the age of patients, comorbity, and treatment. Earlier studies on antibiotic treatment do not indicate favorable effects on the outcome of acute pancreatitis [1, 2, 3]. However these studies were carried before the CT era [4], without the possibility of exactly stratifying pancreatic necrosis as sterile necrosis, infected necrosis and pancreatic abscess [5], and before the discovery that bacterial contamination of pancreatic necrosis is the cause of a significant increase of morbidity and mortality [6]. Furthermore, these studies were also not able to take into account the new advances in antibiotic pancreatic penetration [7, 8], especially during the acute phase of the disease [9].

These achievements have enabled Pederzoli *et al.* to design the first clinical trial on antibiotic prophylaxis in acute pancreatitis with a less empiric approach based on a broad-spectrum antibiotic in which pancreatic penetration at therapeutic minimal inhibitory concentration was proved [10]. In this randomized multicenter study, 74 patients with computed tomographic scans demonstrating necrotizing pancreatitis within 72 hours of onset were assigned to two groups receiving no antibiotic treatment or 0.5 grams of prophylactic imipenem administered intravenously every eight hours for two weeks. Pancreatic sepsis was always detected by means of cultures (percutaneous computed tomography or ultrasound-guided needle aspiration and intraoperative samples). The incidence of pancreatic sepsis was much lower in treated patients (12.2% versus 30.3%, $P<0.01$); however, this study failed to demonstrate a significant reduction in mortality for sepsis even if the mortality in the placebo group (12.1%) was higher than that in the treated group (7.3%). Therefore, the authors recommend prophylactic use of imipenem in patients with acute necrotizing pancreatitis.

After this study, several other multicenter [11, 12, 13, 14], as well as single-center [15, 16, 17, 18], studies were carried out. Except for those of Sainio *et al.* [15] and Luiten *et al.* [11], all these studies failed to demonstrate any significance in the mortality rate between the treated groups in comparison with the placebo groups. Whereas in the Luiten *et al.* study [11], late mortality was significantly reduced using a selective decontamination of the gut, in the Sainio *et al.* study [15], the reduction in mortality was due not only to antibiotic treatment but partly for adequate fluid resuscitation and effective intensive care combined with the correct timing and type of surgical intervention, as suggested by the same authors.

Subsequently, two meta-analyses appeared [19, 20]. The first of these two papers concluded that the use of prophylactic antibiotics in severe alcoholic acute pancreatitis significantly reduces the incidence of severe infection [19]; the second meta-analysis [20] confirmed the results of the previous study regarding the reduction of sepsis in patients with acute necrotizing

pancreatitis irrespective of the etiology, and, even more importantly, was also able to demonstrate that, aggregating the data of the studies of Pederzoli *et al*. [10], Sainio *et al*. [15] and Schwarz *et al*. [16], antibiotic prophylaxis was also able to decrease the mortality. Thus, the authors suggested that prophylaxis with an antibiotic with proven efficacy in necrotic pancreatic tissue should be given to all patients with acute necrotizing pancreatitis.

However, some points have unanswered questions: what is the antibiotic of choice (imipenem [10], cefuroxime [15], ofloxacin plus metronidazole [15])? What is the time-duration of antibiotic prophylaxis? What is the optimal route of antibiotic administration? What are the complications of antibiotic prophylaxis such as incidence of infection with fungi and the possibility of nonsusceptible bacteria? Finally, in the case of primary fungal infection which accounts for percentages ranging from 37 to 74% of patients with necrotizing pancreatitis [21, 22], should antibiotics be given together with prophylactically antifungal therapy?

Another consideration should be taken into account; none of the studies published until recently were carried out as double blind studies. However, the first double blind multicenter study on the use of antibiotic prophylaxis in acute pancreatitis has been now published [23]. In this study, a total sample size of 200 patients was calculated with a power of 90% in order to demonstrate that antibiotic prophylaxis reduces the proportion of patients with infected pancreatic necrosis from 40% of placebo to 20% of combined therapy with ciprofloxacin/ metronidazole. One hundred and 14 patients with acute pancreatitis in combination with a serum C-reactive protein exceeding 150 mg/L and/or necrosis on contrast-enhanced computed tomography scan were enrolled and received either intravenous ciprofloxacin (2x400 mg/day) plus metronidazole (2x500 mg/day) or placebo. Study medication was discontinued and switched to open antibiotic treatment when infectious complications, multiple organ failure sepsis, or systemic inflammatory response syndrome occurred. After half of the planned sample size was recruited, an adaptive interim analysis was performed, and recruitment was stopped because the trend in the incidence of infected pancreatic necrosis was in the opposite direction of the assumptions of the study. Fifty-eight patients received ciprofloxacin/ metronidazole therapy and 56 patients received a placebo. Twelve percent of the ciprofloxacin/metronidazole group developed infected pancreatic necrosis as compared to 9% of the placebo group (P=0.585), and the authors concluded that there is no benefit in antibiotic prophylaxis for protecting against the risk of developing infected pancreatic necrosis. Regarding the secondary endpoints of the study such as incidence of death, incidence of extrapancreatic infection, surgical treatment for necrotizing pancreatitis, duration of stay in the intensive care unit, duration of hospitalization, there were no statistical differences between the treated group and the placebo group; this may be due to the small sample of the subjects enrolled demonstrating that, for these parameters, the study had no adequate statistical power. Some points of this study are not clear; the use of C-reactive protein to stratify necrotizing pancreatitis is questionable. In fact, of the 114 patients who were enrolled in the study, 45 were recruited on the basis of elevated serum C-reactive protein only and, in this group, only six patients developed pancreatic necrosis (13.3%). Furthermore, a high percentage of subjects of the placebo group (26/56, 46%) were treated with antibiotic therapy during the course of the study period and 16 out of 58 (28%) treated subjects received antibiotics different from those of the study protocol; thus, this large crossover rate could have introduced a bias in the study. On the other hand, why did the authors choose antibiotics such as fluoroquinolones which, in a previous clinical study [12], did not demonstrate efficacy similar to imipenem? Finally, how many patients were fed enterally? Enteral nutrition has been demonstrated to decrease the risk of bacterial translocation in patients with severe acute

pancreatitis; enteral feeding repairs the mucosal damage of fasting and started very early, it preserves epithelial integrity and bacterial ecology, thereby helping to maintain gut barrier function [24, 25, 26, 27, 28, 29], but, in this study, there is no mention as to whether or not this procedure was applied.
In conclusion, it cannot not be affirmed on the basis of this study that another myth bites the dust; this study only demonstrate that the road to Rome is too long.

Keywords Antibiotic Prophylaxis; Clinical Trials; Controlled Clinical Trial; Meta-Analysis; Pancreatitis, Acute Necrotizing

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