

## Original Research Article

# Comparison of use and non-use of prophylactic antibiotics for severe acute pancreatitis

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## ABSTRACT

**Background:** Acute pancreatitis is a frequent disease in Chile, with mortality rate of 10-30%. Prophylactic antibiotics administration has been part of severe acute pancreatitis treatment for theoretical prevention of infectious complications and mortality reduction. Yet the available evidence is controversial. The aim of the study was to demonstrate that prophylactic antibiotics do not reduce complications, need for intensive care unit bed or mortality in severe acute pancreatitis.

**Methods:** Randomized clinical trial with simple randomization using a computational table (use or non-use of prophylactic antibiotics) of patients with severe acute pancreatitis. We define severe acute pancreatitis as APACHE II  $\geq 8$ , C-reactive protein  $\geq 150$ . In prophylactic antibiotics use group, ciprofloxacin and metronidazole were administered for 7 days. This preliminary report is presented with 50% of the calculated sample.

**Results:** N=150, two randomized groups; group 1 (n=73), without prophylactic antibiotics use, and group 2 (n=77) with antibiotic prophylaxis use. Twenty-four patients (16%) required intensive care unit bed; twelve in group 1, and twelve in group 2 (p=0.53). Ten patients (6.66%) had some type of complication, one in group 1 and nine in group 2 (p=0.01). The average hospital stay was  $15.7 \pm 9.0$  days in group 1, and  $16.8 \pm 17.9$  days in group 2 (p=0.57). Mortality was four patients (2.66%), one in group 1 and three in group 2 (p=0.33).

**Conclusions:** In this preliminary report, the prophylactic antibiotics use for severe acute pancreatitis was not shown to reduce complications, need for an intensive care unit bed or mortality.

**Keywords:** Acute pancreatitis, Antibiotic prophylaxis, Randomized clinical trial

## INTRODUCTION

Acute pancreatitis (AP) is a frequent pathology and one of the main hospitalizations causes of patients with abdominal pain.<sup>1</sup> Around 80% of patients recover fully in 1 week (2), since it mainly develops as an uncomplicated disease, without infectious events and without requiring intensive treatment. However, 20% of patients present local or systemic complications, with a mortality rate of 10-30%.<sup>3,4</sup> The Atlanta Consensus defines severe acute pancreatitis (SAP) as being morphologically related to extended necrosis of the pancreatic tissue (>30%), infection due to necrosis or abscess formation, and/or

presence of retroperitoneal necrosis of extrapancreatic tissue. Even more important, SAP is identified by the presence of systemic organ complications (pulmonary, renal or hepatic failure) and cardiopulmonary dysfunction (shock).<sup>5,6</sup>

SAP is the only model of prolonged antibiotic prophylaxis. There are many systematic reviews of randomized clinical trials (RCT) that demonstrate the clinical effectiveness of prophylactic antibiotics in pancreatitis that reduce mortality and incidence of infection, whereas other reviews have not found a significant clinical benefit of the use of prophylactic antibiotics.<sup>3,7-11</sup>

In terms of predicting severity, the criteria of the Atlanta consensus have been modified in the clinical guidelines of the United Kingdom, and these modifications consist in considering SAP in patients with an APACHE II  $\geq 8$  or C-reactive protein (CRP)  $\geq 150$ .<sup>12</sup>

In recent decades, the prophylactic administration of antibiotics has been part of the treatment of SAP in our environment for the theoretical prevention of infectious complications and mortality reduction.<sup>12</sup>

We published in the Revista Chilena de Cirujanos the preliminary report with 25% of the sample, where the use of prophylactic antibiotics in SAP did not demonstrate a reduction of local infectious complications, systemic infectious complications, requirement of admission to the intensive care unit (ICU) or mortality.<sup>13</sup>

The aim of the study was to report the results of this interim analysis with 50% of the calculated sample.

## METHODS

### Design

Randomized clinical trial with simple randomization (use or non-use of prophylactic antibiotics). The random allocation was done using a computational table. This was a preliminary report containing 53% of the total estimated sample.

### Population

Patients with SAP evaluated and treated by the biliopancreatic surgery team at the Hospital Dr. Hernán Henríquez Aravena (HHHA) between 01 April 2016 and 30 May 2019.

### Inclusion criteria

All the patients with SAP admitted to the HHHA and treated by the hepatobiliary surgery team were included in the study.

### Exclusion criteria

Patients with following criteria were excluded- (a) mild acute pancreatitis (MAP); (b) who began antibiotic for infection suspicion, since the concept of infection treatment is different from the concept of prophylaxis; (c) who had undergone another antibiotic therapy for another non-pancreatic infected site.

### Management

Patients admitted with a diagnosis of AP were classified according to the APACHE II severity score and the CRP value. Patients with an APACHE II  $\geq 8$ , or CRP  $\geq 150$  (normal value  $<10$  mg/dl) or multiorgan dysfunction were classified as SAP.

Once the SAP diagnosis was confirmed, randomization took place using a simple computational table by the study coordinators.

Ciprofloxacin and metronidazole were used in the group that used prophylactic antibiotics. Their use was ideally orally or by nasogastric intubation: 500 mg of ciprofloxacin (ciprofloxacin, Ascend) every 12 hours and 500 mg of metronidazole (metropast, Pasteur) every 8 hours. Use of intravenous ciprofloxacin and metronidazole was reserved for patients unable to tolerate antibiotic use orally and/or by nasogastric intubation, for example in patients with ileus. The dose of intravenous antibiotics used was 400 mg ciprofloxacin (Ciprolife®, Aculife®) every 12 hours and 500 mg metronidazole (Apiroflex®, Biosano®) every 8 hours. The duration of the antibiotic prophylaxis was left up to the biliopancreatic surgery team, being set at 7 days. The rest of the treatment (nutritional support, transfer to ICU, check-up X-rays, surgery or procedures) did not vary between groups.

### Definition of variables

#### Complications

Measurement as dichotomous variable in terms of presence of complication or not.

#### Local infectious complications

In the case of clinical and/or radiological suspicion of peri-pancreatic infection that requires empiric broad-spectrum antibiotic treatment.

#### Sepsis from a non-pancreatic source

Episodes of sepsis of non-pancreatic origin documented by images or cultures that call for therapeutic procedures or for the antibiotic therapy to be started or changed.

#### Requirement of admission to the intensive care unit (ICU)

This is measured as a dichotomous variable (present or absent) when the reason for admission is organic dysfunction or sepsis.

#### Hospital stay

This is measured as a continuous variable, in days.

#### Mortality

This is measured as a dichotomous variable (present or absent).

### Calculation of sample size

This was done using the EPI INFO program based on the Japanese meta-analysis of Ukai et al, which showed that the infection rate due to necrosis in the group that did not

use antibiotics was 25%, demonstrating a reduction of 10% in the group that used antibiotics.<sup>9</sup> Using a statistical significance level of 95% and a power of 80%, the sample size is 140 patients per group, with a total of 280 patients.

### Statistical tools

The database for the study was prepared in Excel® and the analysis was performed with STATA® version 14.0. Descriptive statistics were used with measures of central tendency and dispersion; analytical statistics were used with the chi-squared or Fisher's exact test for the dichotomous variables and the t-test for the continuous variables. The magnitude of association was measured in odds ratio and absolute risk.

## RESULTS

The study was comprised of 150 patients (50% of the total sample), divided into two randomized groups: group 1 (non-use of prophylactic antibiotics) contained 73 patients, and group 2 (use of antibiotic prophylaxis) contained 77 patients. The average age of the total group (N=150) was 59.4±19 years; the average age in group 1 was 58±19.2 years and in group 2 it was 60±18.6 years (p=0.52) (Table 1). The distribution by gender showed a women predominance in the total group with 56.6% (N=85): group 1 had 60.2% (N=44) women, and group 2 had 51.9% (N=40) (p=0.30) (Table 1).

The main etiology was lithiasis, being 83.3% of the total group with a similar distribution between the two groups (84.9% and 81.8%, respectively). The average CRP (mg/dl) on admission of all the patients was 174±119. In group 1 it was 196±108, and in group 2 it was 151±106 (p=0.88). The average CRP at 48 hours was 179±110. In group 1 it was 162.4±109.6, and in group 2 it was 195.1±109.5 (p=0.06) (Table 2).

The APACHE II average on admission of all the patients was 7.9±4.3. In group 1 it was 7.4±4.1, and in group 2 it was 8.3±4.4 (p= 0.56). The average APACHE II at 48 hours was 8±5. In group 1 it was 7±4.5, and in group 2 it was 8±5.4 (p=0.22) (Table 2).

About the outcome variables (Table 3), 24 patients needed a bed at the ICU (16%)- 12 patients from the group without antibiotics and 12 patients from the group with antibiotics (p=0.53). The average stay at the ICU of all the patients was 11±15.7 days. In group 1 the average was 8±7.8 days and in group 2 14±20.7 days (p= 0.57).

Ten patients (6.6%) had some type of complication related to SAP, one patient in group 1 and nine in group 2 (p=0.01). The average hospital stay of all the patients was 16.3±14.2 days. In group 1 it was 15.7±9.0 days, and in group 2 it was 16.8±17.9 days (p=0.57). In mortality terms, four patients died (2.6% patients) during the study, one patient was in the group that did not use antibiotics and three patients in the group that did (p= 0.33).

**Table 1: General characteristics of the cohort.**

General characteristics	Group 1 (n=73)	Group 2 (n=77)	P value
Age (mean±SD) (years)	58±19.21	60±18.86	0.52
Femenine gender (%)	60.2	51.9	0.30
Lithiasic (%)	84.9	81.8	0.38

Note: group 1 = without use of antibiotics; group 2: with use of antibiotics.

**Table 2: Comparison of diagnostic and prognostic indicators.**

Indicators	Group 1 (n=73)	Group 2 (n=77)	P value
Admission APACHE II	7.4±4.1	8.3±4.4	0.56
48 hours APACHE II	7±4.5	8±5.4	0.22
Admission CRP (mg/dl)	196±108	151±106	0.88
48 hours CRP (mg/dl)	162.4±109.6	195.1±109.5	0.06

Note: group 1 = without use of antibiotics; group 2: with use of antibiotics.

**Table 3: Cohort outcome variables.**

Cohort outcome	Group 1 (n=73)	Group 2 (n=77)	P value
Local complications	1	9	19
Stay at ICU	12	12	24
Hospital stay (mean±SD, days)	15.7±9.0	16.8±17.9	16.3±14.2
Mortality	1	3	4

Note: group 1 = without use of antibiotics; group 2: with use of antibiotics.

## DISCUSSION

Mortality in severe acute pancreatitis is clearly associated with infectious complications and thus the administration

of prophylactic antibiotics has been part of SAP management for decades. However, the controversy continues due to insufficient evidence.<sup>3,4</sup> The evolution of pancreatitis suggests that the initial necrosis experiences

liquefaction over time and then can be reabsorbed and form a post-necrotic collection. This is why from the theoretical point of view, if we manage to reduce the infection due to necrosis, we can have fewer local complications and lower mortality. There is clear evidence that patients with local complications present a higher morbidity and mortality rate, in part due to the greater risk of infection from these complications.<sup>2,6,7</sup>

The antibiotics used in SAP prophylaxis must have two conditions: cover the most common bacteria involved in the infected necrosis and local complications of patients with SAP, and adequately penetrate the pancreatic tissue. The most commonly involved germs are gram-negative and anaerobic bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* and *Bacteroides*.<sup>2,3</sup>

In recent years there have been changes made in SAP treatment, reducing the local and systemic complications as well as mortality. These measures include the use of prophylactic antibiotics. However, their real role is unclear.<sup>12</sup>

A study published in 2018 used ciprofloxacin associated with metronidazole as antibiotic prophylaxis in acute pancreatitis and reported that there was no significant clinical improvement compared to the group that did not use antibiotic prophylaxis.<sup>14</sup>

Recent studies have reported that the use of antibiotic prophylaxis in SAP may be associated with the development of invasive pancreatic candidiasis; in addition, they did not demonstrate any reduction in related complications.<sup>15</sup> Other studies have reported not only that the use of antibiotic prophylaxis has no significant clinical benefit, but also that it is associated with an increased intrahospital infection risk; therefore, the use of antibiotic treatment must be reserved only for patients with local infection or sepsis.<sup>16,17</sup> These numbers are consistent with our study, where we reported that the group that received antibiotic prophylaxis had more local complications than the group that did not use prophylaxis ( $p=0.01$ ) (Table 3).

There is only one RCT that has shown the usefulness of prophylactic antibiotics with carbapenems in patients with SAP (5). Among the controversies surrounding the use of prophylactic antibiotics in SAP are the economic cost and the prolonged exposure effect to a certain antibiotic therapy, which can put pressure on the ecosystem and increase bacteria resistant to these antibiotics. Quinolones have been involved in the generation of resistant bacteria due to various genetic and non-genetic mechanisms. Therefore, prolonged exposure (in time and number of patients) to a prophylactic therapy with quinolones could cause an increase in multidrug-resistant bacteria. We do not know if it is cause or effect, or only coincidence, but we have noted and reported an increase in the multidrug-resistant bacteria number in recent years in the cultures of pancreatic infections in patients with SAP.<sup>13</sup>

The logical question of why carbapenems are not used prophylactically raises an ethical and scientific discussion, since carbapenems are the basis of the treatment of multidrug-resistant infections, particularly of bacteria with extended-spectrum beta-lactamases (ESBL), a problem in global bacterial ecology. Then, how to use the only treatment available for these bacteria as prophylaxis?

The other point is the true impact of a single aspect (prophylactic antibiotics) on a disease, the evolution of which is multifactorial, and whose mortality is influenced by factors such as reanimation at the onset of the disease, early enteral feeding, percentage and location of the necrosis and others have an influence.<sup>2-10,17</sup>

We wanted to report the results of our study after collecting 50% of the sample. The table comparing the groups shows that they are perfectly comparable (Tables 1 and 2). After this study, we propose reserving the use of antibiotics only for suspicion or confirmation of pancreatic or extra-pancreatic infection, which has a tremendous economic impact, mainly on public hospitals, and it will have a significant impact on the different hospital ecosystems.

## CONCLUSION

Our preliminary report with 50% of the sample shows that the use of prophylactic antibiotics in SAP does not reduce the local and/or systemic infectious complications, need for a bed in the ICU or mortality. This trend must be demonstrated in future reports.

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