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Procalcitonin-guided therapy may reduce length of antibiotic treatment in intensive care unit patients with secondary peritonitis: A multicenter retrospective study

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ABSTRACT

Purpose: Because procalcitonin (PCT) might be surrogate for antimicrobial discontinuation in general intensive care units (ICUs), this study explored its use for secondary peritonitis in 4 surgical ICUs (SICUs).
Methods: A retrospective study including all consecutive patients with secondary peritonitis, controlled infection source, requiring surgery, and at least 48-hour SICU admission was performed (June 2012–June 2013). Patients were divided following notations in medical records into PCT-guided (notation of PCT-based antibiotic discontinuation) and non–PCT-guided (no notation) groups.
Results: A total of 121 patients (52 PCT-guided, 69 non–PCT-guided) were included. No differences in clinical scores, biomarkers, or septic shock (30 [57.7%] PCT-guided vs 40 [58.0%] non–PCT-guided) were found. Length of intra-SICU (median, 5.0 days; both groups) or in-hospital (median, 20.0 vs 17.5 days) stay, and mortality intra-SICU (9.6% vs 13.0%), 28-day (15.4% vs 20.3%), or in-hospital (19.2% vs 29.0%) were not significantly different (PCT-guided vs non–PCT-guided). In septic shock patients, no mortality differences were found (PCT-guided vs non–PCT-guided): 16.7% vs 22.5% (intra-SICU), 26.7% vs 32.5% (28-day), and 33.3% vs 42.5% (in-hospital). Treatment was shorter in the PCT-guided group (5.1 ± 2.1 vs 10.2 ± 3.7 days, $P < .001$), without differences between patients with and without septic shock.
Conclusion: Procalcitonin guidance produced 50% reduction in antibiotic duration ($P < .001$, log-rank test).

1. Introduction

Duration of antibiotic treatment of complicated intra-abdominal infections is controversial, without wide consensus due to the absence of controlled studies supporting adequate scientific evidence [1]. Different scientific societies and authors recommend short treatments [2–4]; however, the use of short antibiotic treatment schedules is far from consolidated, most surgeons considering 7 days as the minimal duration for the treatment of complicated intra-abdominal infections [1]. Among strategies aimed to improve antibiotic use, not only de-escalation of therapy is advocated [5] but also the reduction in the length of treatment. Appropriately shortening treatment duration is an important aspect for decreasing antibiotic-associated costs and selective pressures for resistant organisms in the intensive care unit (ICU) and improving outcomes [6].

In complicated intra-abdominal infections, 2 parameters have been used to limit treatment duration: intraoperatory findings [7,8] and clinical evolution [9,10]. A third strategy that has been postulated is the use of biomarkers in addition to microbiological and clinical indicators. In the ICU, serial procalcitonin (PCT) measurements might be used as surrogate to facilitate the early discontinuation of antimicrobials, using a PCT threshold of less than 0.5 ng/mL or a decrease of at least 80% [11,12]. It has been postulated that physicians feel more confident in discontinuing antibiotic therapy when PCT levels decrease because PCT concentrations parallel severity of infection [5,13]. Procalcitonin levels rise during bacterial infections [14] but only minimally in other inflammatory reactions [15] and surgical trauma [16], this representing

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an advantage for treatment monitoring in intra-abdominal infections. Some studies on PCT-guided antibiotic therapy have included patients with complicated intra-abdominal infections [12,17,18], although these infections represent the second most common cause of septic shock [19]. However, only one recent study was focused on a homogeneous group with all patients presenting with community-acquired secondary peritonitis [20].

Nowadays, within a single hospital unit, some attending physicians feel more confident in discontinuing antibiotic therapy based on PCT concentrations as reported for sepsis/septic shock, whereas others base their decisions on their own medical criteria and treatment recommendations from guidelines. The aim of the present study was to explore length of treatment following both criteria in patients with secondary peritonitis admitted to surgical ICUs (SICUs).

2. Methods

A multicenter observational study was performed from June 2012 to June 2013 in 4 SICUs belonging to 4 Spanish hospitals. In all these units, among other parameters, in patients with severe infection, PCT and C-reactive protein (CRP) are daily determined during the infectious process. Decision to de-escalate antibiotic treatment in the unit's treatment protocols is left to the discretion of the attending physician. In their daily practice, some of the staff physicians at these SICUs followed the algorithm used by Bouadma et al [12] that consists of stopping antibiotic treatment when the PCT value reaches less than 0.5 ng/mL or has decreased at least 80% from the peak concentration, as proposed by the Perioperative Infection Group of the Spanish Anesthesiology and Critical Care Society. A retrospective analysis was performed on prospectively acquired data recorded in medical records as part of daily routine care (practice-based analysis) of all consecutive adult patients with secondary peritonitis and controlled infection source requiring surgery and SICU admission for at least 48 hours. Patients with tertiary peritonitis were not considered in the analysis. The informed consent was not obtained due to the observational nature of the study. Patient records/information was anonymized and de-identified prior to analysis. Ethical approval for this study (Ethical Committee No. HULP 3529) was provided by the Ethical Committee of Hospital Universitario La Paz, Madrid, Spain, on April 11, 2012.

Medical records were reviewed and patients divided into 2 groups: patients with notation in their medical records that antibiotic treatment was stopped due to PCT values were grouped in the PCT-guided study group, and patients without notation of PCT guidance were grouped in the non–PCT-guided group. Demographic and clinical data (comorbidities, need for mechanical ventilation, renal replacement therapy, etc), microbiological data (results of intra-abdominal cultures and of periodical rectal swabs for colonization surveillance), antibiotic treatment (duration and drugs used), length of stay (intra-SICU and in-hospital stay), and mortality (intra-SICU, 28-day, and in-hospital mortality) were recorded. The Simplified Acute Physiology Score (SAPS II) [21] and the Sequential Organ Failure Assessment (SOFA) [22] were calculated with data in the first 24 hours and also with data recorded 72 hours after admission in the case of the SOFA score. Values of CRP, lactate, and PCT (Thermo Fisher Scientific Inc, Madrid, Spain) were daily determined, and those obtained 24, 48, and 72 hours after admission were recorded to calculate peak values (the highest value of each biomarker in the first 72 hours for each patient).

Comparisons between proportions were performed by the χ^2 test and the Fisher exact test, when necessary. For quantitative variables, because data did not show normality in the Kolmogorov-Smirnoff test, the Kruskal-Wallis and Mann-Whitney tests, when necessary, were used. All variables were compared between the PCT-guided and the non–PCT-guided groups. In addition, patients were divided into 2 groups according to the presence or not of septic shock, both for the total study population and for the PCT-guided and non–PCT-guided study groups, and treatment duration and mortality were compared between groups. An ordinal log-rank test was used to compare antibiotic treatment duration between the PCT-guided and the non–PCT-guided groups. Statistical analyses were performed using SPSS v 14 programme (SPSS Inc, Chicago Ill).

3. Results

A total of 121 patients were included. Fig. 1 shows the diagram of the study population, and Table 1 shows demographics, clinical data, and peak values of biomarkers by study group. Up to 56.2% of patients were at least 65 years old and 38.0% at least 75 years old, without differences between study groups. Approximately 50% cases involved the colon as surgical site. The infection was nosocomial in 40.4% patients in the PCT-guided group and 39.1% in the non–PCT-guided group ($P = .992$). Overall, the most frequent comorbidities were oncologic metastasis (9/121 patients; 7.4%), chronic respiratory disease requiring domiciliary oxygen therapy (8/121; 6.6%), congestive heart disease (7/121; 5.8%), and hematologic disease, steroid dependence, chemotherapy, other immunosuppressions, and chronic renal replacement therapy (4/121; 3.3% each), without differences between groups for each comorbidity. Up to 29.8% patients presented at least 1 comorbidity, with a significantly higher number of patients in the non–PCT-guided group presenting with comorbidities. No differences in values of clinical scores or biomarkers, or in the percentage of patients developing septic shock ($P = .975$) were found between groups.

Table 2 includes results of diagnostic microbiological cultures, showing frequencies of isolates among the 121 study patients. A total of 70 (57.9%) patients had positive cultures, 74.3% of them polymicrobial, without differences between study groups. Among these 70 positive cultures, the most frequent species isolated was *Escherichia coli* (37/70 patients; 52.9%) followed by *Enterococcus* spp (34/70; 48.6%), anaerobes (29/70; 41.4%), *Streptococcus* spp (22/70; 31.4%), and *Klebsiella* spp (8/70; 11.5%). Four *E coli* isolates (4/37; 10.8%) and 2 (2/8; 25%) *Klebsiella* spp isolates produced extended-spectrum β-lactamases (ESBLs). All isolates were recovered from intra-abdominal samples, except 4 *E coli*, 2 *Klebsiella* spp, and 1 *Bacteroides fragilis* isolates recovered from blood cultures.

Cultures of rectal swabs for colonization surveillance yielded growth of multidrug resistant bacteria in 17 (12 in the non-PCT group and 5 in the PCT group) of 121 patients (14.0%), without differences between study groups: 14 ESBL-producing enterobacteria (10 in the non-PCT and 4 in the PCT group), 2 *Stenotrophomonas* spp (1 in each group), and 1 *Acinetobacter* spp (in the non-PCT group).

Table 3 shows antimicrobials used by study group. A total of 42 (34.7%) patients received single-drug therapy; 24 (19.8%), therapy with 2 compounds; 42 (34.7%), therapy with 3 compounds; and 13 (10.7%), therapy with at least 4 compounds, without differences by study group. Neither differences were found in antibiotics used by study group, with carbapenems being the most frequently used compounds (62.8%): 42 patients receiving meropenem and 34 patients receiving ertapenem,

Antifungals were administered to 39.7% patients. Micafungin was administered in 54.2% (26/48) patients receiving antifungals, anidulafungin in 20.8% (10/48), fluconazole in 18.8% (9/48), and caspofungin in 12.5% (6/48) patients. A significant higher number of patients in the PCT-guided group were treated with antifungals (50.0% vs 31.9%, $P = .043$).

Among the total 70 patients with septic shock, treatment with tigecycline, meropenem, and antifungals was significantly more frequent (compared with patients not presenting with septic shock): 55.7% vs 29.4% ($P = .004$), 44.3% vs 21.6%, ($P = .010$), and 37.1% vs 19.6% ($P = .037$), respectively, whereas ertapenem was more frequently used in patients not presenting with septic shock (20.0% vs 41.2%, $P = .011$). These significant differences were maintained within the PCT-guided group, with more frequent administration of tigecycline (56.7% vs 22.7%, $P = .014$) and antifungals (50.0% vs 22.7%, $P = .046$) in patients