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A procalcitonin-based guideline promotes shorter duration of antibiotic use safely in acute pancreatitis

KEYWORDS
Acute pancreatitis;
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To the editor,

We read with interest the article by Hoeboer et al.[1] Like critically ill patients in the intensive care unit (ICU), patients with acute pancreatitis (AP) develops systemic inflammatory response syndrome, which is difficult to distinguish from sepsis.[2] Hence, physicians often prescribe broad-spectrum prophylactic antibiotics for fear of undertreatment. This is exacerbated by the fact that early studies have reported findings in favor of prophylactic antibiotics in AP.[3,4] However, these positive findings have been attributed to poor study designs, and recent randomized trials have shown that routine antibiotic prophylaxis did not confer benefits, but resulted in increased hospitalization costs and antimicrobial resistance.[5–7]

In light of the current situation, the Singapore General Hospital (SGH) Antimicrobial Stewardship Team (ASP) developed a procalcitonin-based guideline for AP in collaboration with the General Surgery Department, to guide prudent antibiotic prescribing (Fig. 1). Procalcitonin was employed as it can predict bacterial infections in critically ill patients and allowed early diagnosis of infected necrosis in AP.[8,9] While the guideline was widely implemented in SGH, adherence was not enforced and eventual adherence was autonomously decided by the primary physician. Hence, we aim to evaluate the adherence to and impact of the guideline on antibiotic utilization and patient outcomes.

A retrospective study was performed for all patients admitted from January–December 2011 with a primary diagnosis of AP (ICD-9 code 577.0). Patients were excluded if they were severely immunosuppressed; for patients with recurrent AP, only the first episode was included. Included patients were segregated into two groups: adherence (Group I) and non-adherence to protocol (Group II). The allocation of patients to either group was decided independently by the two study members; if a lack of consensus was observed, the opinion of a third member was sought. The study was approved by the institutional ethics committee.

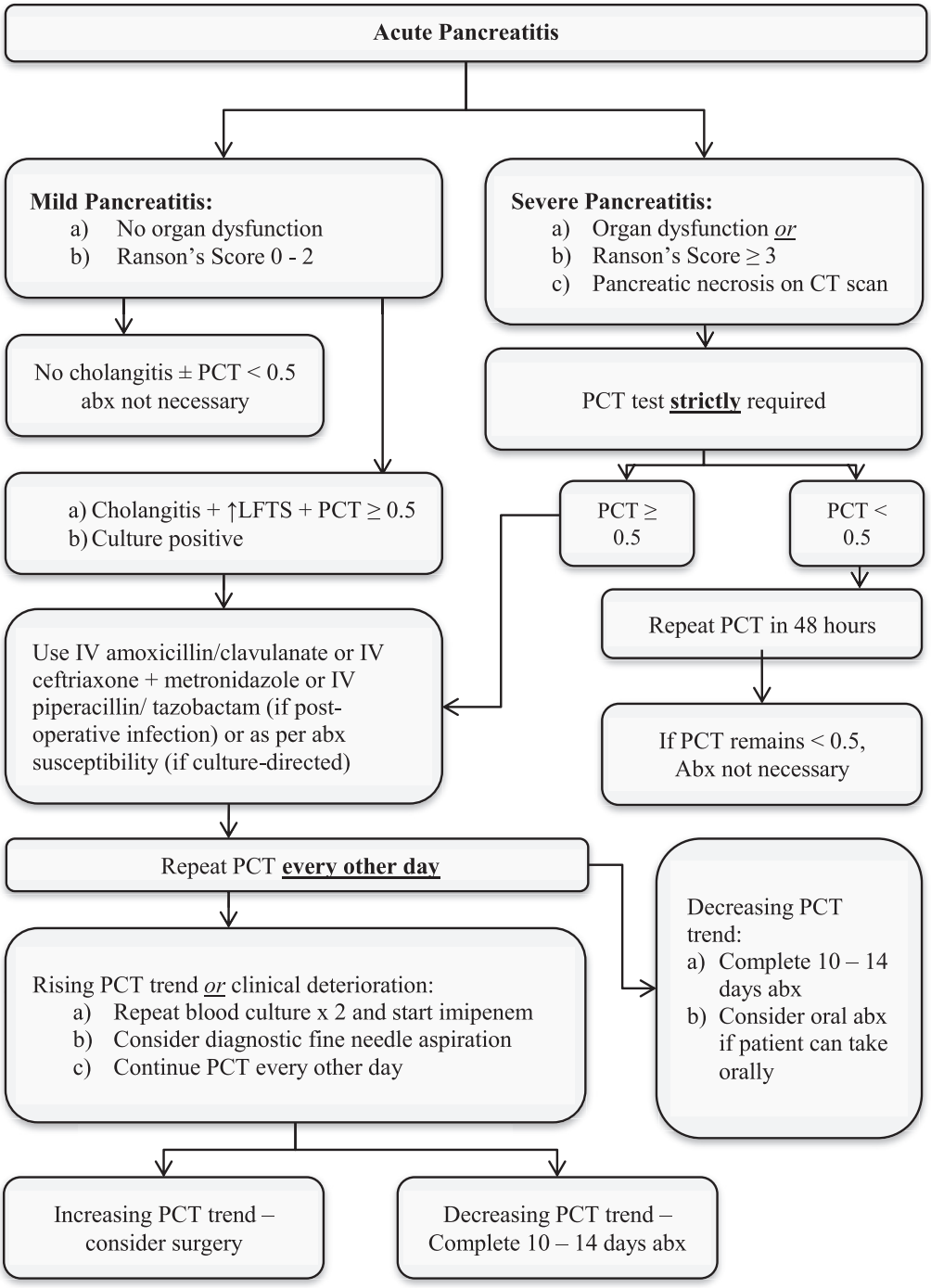
The primary outcome was difference in intravenous antibiotic use (days of therapy); in addition, an adjusted outcome was estimated using multi-variable regression, to correct for differences in baseline. Secondary outcomes included differences in 30-day crude mortality, days to enteral feeding, days to resolution of fever and white blood cell (WBC) count. Sample size requirements were estimated based on the PRORATA trial; assuming a mean of 10.8 days therapy in the non-adherence group, approximately 95 patients per group provided power of 80% (two-sided $\alpha = 0.05$) to detect a three-day difference.[10]

A total of 225 patients were included, with less than half managed in adherence to the guideline (43.1% in Group I, 56.9% in Group II) (Table 1). The most common reasons for non-adherence included initiation of antibiotics without measuring procalcitonin (73.4%) and antibiotic prescription despite low procalcitonin values (14.8%). Approximately one-third of the patients in both groups developed severe pancreatitis (33.0% in Group I, 38.3% in Group II). Baseline demographics were similar for both groups in terms of age, length of hospitalization, APACHE II score, and severity of AP (Ranson's score $\geq$3). There was, however, significantly higher incidence of previous antibiotic use ($p = 0.014$) and presence of co-morbidities ($p = 0.024$) in Group I. There was also differences in etiology of AP ($p = 0.001$), with idiopathic (38.1%) and gallstone pancreatitis (59.4%) being the predominant etiology in Group I and II respectively.

Upon comparing the duration of overall antibiotic use, the mean unadjusted duration of antibiotic prescription in Group I was significantly shorter [mean difference = −3.03 days ($p < 0.001$)] (Table 1). When the antibiotics were individually analyzed, the duration of ceftriaxone (mean difference = −2.50 days, $p < 0.001$) and metronidazole (mean difference = −2.98 days, $p < 0.001$) were significantly shorter in Group I. Similar results were observed after correcting for potential confounders (antibiotics use within three months, presence of co-morbidities, etiology of pancreatitis, presence of necrotizing pancreatitis, and 48 h Ranson's score). After adjustment, the adjusted duration of total antibiotic use in Group I was significantly shorter (adjusted mean difference = −2.77 days, $p < 0.001$). Likewise, the adjusted duration of ceftriaxone and metronidazole also remained significantly shorter in the Group I.

Overall, 30-day crude mortality was low; one (1.0%) patient died from liver cirrhosis in Group I, while three (2.3%) died from severe AP in Group II ($p = 0.377$). There were no significant differences in the incidence of crude 30-day mortality, ICU stay and days to enteral feeding. A notable number of patients developed fever (26.8% in Group I, 40.6% in Group II) and leukocytosis (64.9% in Group I, 76.6% in Group II); however, there were no significant differences in days to resolution of fever or WBC count.

In our study, we observed moderate adherence to the procalcitonin-based guideline in AP patients. It is noteworthy to highlight that baseline APACHE II score was not significantly different between the two groups, implying that inappropriate antibiotic prescription was not confined



Abbreviations used in Figure 1: Abx – antibiotics, CT – computed tomography, IV – intravenous, LFTs – liver function tests, PCT - procalcitonin

Fig. 1 Proposed guideline for management of patients with acute pancreatitis.

to sicker patients. Despite the moderate adherence, our findings suggested that management of AP patients in adherence to the guideline resulted in a significantly shorter duration of antibiotic use without compromising outcomes. This is especially evident in the prescription of ceftriaxone and metronidazole, which were, incidentally, the "work-horse" antibiotics for treatment of intra-abdominal infections in SGH.

There are several advantages to our guideline. Firstly, it acknowledged the need for differential management in patients with mild and severe pancreatitis; in patients with mild pancreatitis, procalcitonin were not dictated. In