



Journal Summary: Procalcitonin Levels to Govern Antibiotic Use in Acute Pancreatitis: Are We There Yet?

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Brief Overview of the Study

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas due to different etiologies.¹ Severe AP occurs in around 20% of cases with high mortality of 20 to 40%.² However, the course of the disease is not uniform, and the dynamics change with the phase of illness. The initial phase entails the sterile “inflammatory” cytokine storm leading to systemic complications, while the later “infective” phase can lead to sepsis.³ Organ failure (OF), a key determinant of outcome in AP, can be early due to an inflammatory burst (primary OF) or late due to infective complications (secondary OF). Evidently, the management of the early phase would be organ support, and that of the later phase is sepsis management in a “step-up” approach starting with antibiotics. Unfortunately, in a real clinical scenario, it is not that simple, as there is no water-tight demarcation line between the two phases. Both the “sterile” and “infective” phase would manifest with the systemic inflammatory response. Moreover, cholangitis, cholecystitis, and extra-pancreatic infection can complicate the picture further. As a result, prophylactic antibiotic use is rampant but is not associated with better outcomes.⁴ Recent analysis has suggested that there is more than 50% overuse of antibiotics in AP worldwide⁵ and more than 80% in Asian countries. Inadvertent antibiotic use can lead to an increased risk of antibiotic-resistant strains, *Clostridium difficile* infection, fungal infection, longer hospital stay, and higher healthcare cost.

While multiple early biomarkers for predicting the severity of AP have been extensively studied,⁶ limited data exist on the prediction of infective complications. Procalcitonin (PCT) is a precursor of calcitonin and released from hepatocytes,

thyroid, and peripheral monocytes. It can be easily measured in serum sample and acts as a surrogate marker of bacterial infection and sepsis.⁷ Early values of PCT have been able to predict the risk of future development of infected pancreatic necrosis in some studies.⁸ This has been utilized as a guide for antibiotic stewardship in various sepsis studies.⁹ However, limited data are available on the use of PCT for antibiotic stewardship in AP.¹⁰ In the current study, Siriwardena et al¹¹ evaluated PCT as a tool to guide antibiotics therapy in AP.

In this single-center, randomized controlled trial,¹¹ patients diagnosed with AP were randomized into PCT-guided care and standard of care for use of antibiotics. In the PCT-guided arm, a serum PCT cutoff level of 1.0 ng/mL was considered for start of antibiotics. Serial levels were measured at 0, 4, 7 days, and weekly thereafter. A total of 260 patients were enrolled to receive either PCT-guided care ($n=132$) or standard care ($n=128$). The patients were enrolled in the study at a median of 2.1 days from symptom onset with 58% having mild AP. The primary outcome of use of antibiotics was noted in 45% of patients in the PCT arm compared with 63% in the standard care arm ($p=0.0071$), with shorter duration of use (4.5 vs. 5.8 days) while having equivalent secondary infection rates, hospital stay, readmission rates, or mortality. On sensitivity analysis, there was reduced risk of antibiotic use in patients with mild AP using the PCT-guided strategy, but the same was not true for moderate or severe AP. The study encompassed the coronavirus disease 2019 (COVID-19) period. The authors found that PCT-guided strategy had reduced risk of antibiotic use (risk difference: -20.5% ; $p=0.0014$) in the pre-COVID-19 era, but not since COVID-19.

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Implications of the Study

This is the largest study of its kind to have addressed a key issue in the management of AP, that is, an objective marker to guide antibiotic use. The authors demonstrated that serum PCT levels can be used to guide when to start antibiotics or when to stop it and this strategy could help reduce antibiotic use in AP without altering the outcome. After adjusting for the use of antibiotic prophylaxis for indications such as interventional procedures, PCT-guided management further reduces the risk of antibiotic use. This could translate to reduction in the use of antibiotics and in turn its harmful effects. The clinical picture of AP is a complex interplay of multiple inflammatory and infective processes and often confuses clinical decision making. These findings could open the path for development of a more objective strategy of antibiotic use in AP rather than a pure subjective “physician-dependent” management decision.

Caveats

While the study findings are promising, there are certain caveats to its generalized interpretation.

1. The median symptom duration, prior to admission, was 2 days in the current study. While the authors did not mention the median time for starting of antibiotics, this evidently fell in the “inflammatory” phase when routine use of antibiotics is not recommended.¹² Additionally, using PCT, which is also an AP severity marker,⁶ early in the disease course to demarcate presence of “infection” could be tricky.
2. PCT-guided strategy did not reduce the risk of antibiotic use in moderate/severe pancreatitis, the key subgroup which is prone to develop infections. This could be explained by the low number of moderate/severe AP cases in this study. Mild AP was the largest cohort in the current study (58%) who do not usually develop late infective complications.² An effective “infection marker,” such as was intended through PCT guidance is more needed for determining the timing of antibiotics in moderate/severe AP cohort.
3. In the current study, interestingly, there was 30% clinician over-ride of the protocol in the PCT-arm. This could have made the study grossly under-powered per-protocol. This

highlights the fact, as mentioned earlier, that lack of an objective antibiotic policy biases the clinician decision-making. Physician feels it “safer” to use antibiotics, even in the first week of illness, as was noted in the current study and this proportion would be even higher in real world scenario. Additionally, 14% patients were already on antibiotics at admission in this study which could have confounded the outcome.

4. A key aim of any antibiotic stewardship program is to reduce the chances of resistance development and shorten hospital stay. However, development of hospital acquired infections or hospital stay was not different between the two arms in the current study. This could be due to the high proportion of mild cases and early disease phase in the current study.
5. In this study, pre-COVID-19 phase did show antibiotic-use difference between the two strategies ($p = 0.0014$), but the COVID-19 recruitment period failed to show any difference ($p = 0.99$). AP with COVID-19 infection has been shown to have higher mortality, attributable to the severity of COVID-19 infection.¹³ Evidently more patients would have received antibiotics during this period for COVID-19 and thus, deviate from the intended protocol. This could have been a significant confounder among patients recruited during this period.

The pros and cons of the use of PCT in AP management have been summarized in ► **Table 1**.

Future Direction

While mild AP is more common, it is the severe form of the disease with the development of local complications that are of major concern in the management of AP. Infected pancreatic necrosis is one of the dreaded complications of necrotizing AP and the appropriate time and mode of intervention could alter the outcome in such cases. PCT can be an effective “infection marker” and hence, its level dynamics would be more relevant in AP cases admitted for some time in the hospital and at risk for infective complications. In the author’s institute, a prospective analysis has shown that raised PCT at baseline was associated with poorer outcomes in patients with infected pancreatic necrosis. Moreover, failure in reduction of its levels optimally after intervention can prelude to high mortality.¹⁴ Thus, the study by

Table 1 Procalcitonin use in the management of acute pancreatitis

Advantages	Caveats
Objective marker of infection—can guide decision for antibiotics initiation	Early acute pancreatitis—procalcitonin levels can rise due to inflammatory response. Likely would be more beneficial in the later “infective phase”
Serial levels—can help decide escalation or de-escalation of therapy	Lack of existing “antibiotics use” policy in acute pancreatitis—subjective physician assessment may override objective “infection markers”
Can help achieve a target of antibiotic stewardship in the management of acute pancreatitis	Underlying renal dysfunction can cause falsely high values

Siriwardena et al¹¹ has paved the way for larger well-designed studies to explore the role of PCT in guiding antibiotic policy in AP, more probably for the later infective phase.

Ethical Statement

Not applicable.

Author Contributions

J.S. has contributed to conception, data interpretation, drafting of the manuscript, and final approval of the manuscript.

Data Availability Statement

There is no data associated with this work.

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Conflict of Interest

None declared.

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