A retrospective cohort study of the effect of rapid versus delayed-result procalcitonin testing on antibiotic use at a community hospital

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Abstract

Background Procalcitonin is a serum biomarker used to distinguish bacterial infection from viral or noninfectious syndromes. Primary literature shows mixed data on use of procalcitonin for de-escalation of antimicrobials. Delays in test results of send-out procalcitonin assays may result in prolonged antimicrobial durations. It is unknown whether availability of rapid-result assays may shorten time to antibiotic de-escalation.

Aim This retrospective, cohort study compared antibiotic durations of treatment between groups with rapid-result versus delayed send-out, procalcitonin test modality.

This study was exempt from Ethics Committee Approval, as determined by the Institutional Review Board at the study site.

Method Adult hospitalized patients were included if they had at least one procalcitonin test performed during the study period. The primary outcome compared mean duration of antimicrobial therapy between groups receiving a rapid-result procalcitonin test and a send-out test. Secondary outcomes included incidence of Clostridiodes difficile infection, mention of procalcitonin testing in the electronic medical record in reference to antimicrobial therapy decision making, and presence of comorbidities which affect procalcitonin levels independent of infection.

Results A total of 350 lab results were analyzed. The duration of antimicrobial treatment between groups was not statistically different with the median duration of treatment in the send-out group being 2.95 days compared to 3.35 in the rapid result group, \( p = 0.856 \). Patient comorbidities with potential to lead to a noninfectious elevation or falsely high level of procalcitonin were common.

Conclusion Use of a rapid-result procalcitonin assay does not reduce hospital antimicrobial therapy duration as compared with send-out testing.

Keywords Antimicrobial use · Antimicrobial stewardship · Procalcitonin

Impact Statements

- Studies reporting on the utility of procalcitonin testing to reduce antibiotic days have yielded mixed results.
- Timely lab results are necessary to aid in decision-making regarding antibiotic use, and procalcitonin send-out lab tests may result in delayed antibiotic de-escalation.
- The results of this study demonstrate that availability of rapid procalcitonin test results did not reduce duration of antibiotic use at a large tertiary care community teaching hospital

Introduction

Procalcitonin (PCT) is a serum biomarker that is used to distinguish bacterial infection from other viral or inflammatory causes of infection. PCT levels typically increase six to twelve hours following initial bacterial infections. PCT can also be elevated in non-infectious inflammatory conditions such as trauma, burn, carcinoma, acute or chronic renal disease, cardiogenic shock [1]. The US Food and Drug
Administration approved PCT testing in 2016 to assess sepsis progression and 28-day mortality as well as in 2017 to guide antibiotic therapy in patients with acute respiratory infections [2, 3]. The 2019 American Thoracic Society and Infectious Diseases Society of America community-acquired pneumonia guidelines recommend empiric antimicrobial therapy in all adults with suspected bacterial pneumonia regardless of initial PCT and do not address its use as a tool to guide antibiotic de-escalation for pneumonia. The 2017 Surviving Sepsis campaign does support the measurement of PCT to shorten the duration of antimicrobial therapy in septic patients and supports use of PCT to stop empiric antimicrobials in patients with limited clinical evidence of infection [4]. There is currently a gap in cohesive data surrounding role of PCT monitoring as a clinical indicator of appropriate antimicrobial use in a variety of patient populations. Many clinical organizations have varying recommendations regarding the use of PCT testing. Most recommend that its use should be limited as an adjunct to clinical judgment when de-escalating antimicrobial therapy [4–6]. Laboratory costs should also be taken into consideration when using PCT as an adjunct to clinical judgment as it can add to unnecessary healthcare expenditures when its use is not aligned with guideline recommendations.

Current primary literature shows varying data regarding the use of serial PCT measures to deescalate antimicrobial therapies which creates ambiguity surrounding its utility for this purpose. While some studies have indicated that PCT–guided antimicrobial therapy helps decrease patient antibiotic exposure, others have identified flaws with this test modality such as lack of reliability in patients with sepsis and with certain comorbidities such as renal insufficiency. As an example, results from a study conducted by Christ-Crain M, et al. showed a 55% reduction in duration of antimicrobial therapy when using a PCT guided algorithm compared to standard of care [7]. Some limitations of many of the studies that addressed PCT protocol implementation are as follows; first in many of the trials comparing PCT protocols with standard of care for antimicrobial therapy utilization, a large proportion of prescribers overrode the PCT algorithm in the intervention group and prescribed based on clinical judgment. Second, many of these studies had extensive exclusion criteria including patients who developed sepsis during their stay, immunosuppressed individuals, and individuals who were critically ill, which represent a large population of PCT use at our institution [8–12]. Pointing out these limitations is important because institutions that do not outline specific criteria for whom to use PCT–guided therapy are at risk for resource wasting, increasing burden of testing on institutional laboratories, and increased costs to patients and health systems. A 2019 meta-analysis by Pepper DJ, et al. found that while a PCT–guided algorithm did decrease mortality in some patients, PCT–guided antibiotic discontinuation did not significantly improve survival in trials that included only critically ill patients with sepsis [13]. Another 2019 meta-analysis by Peng F, et al. showed that PCT–guided antimicrobial therapy did not decrease mortality in critically ill patients [14]. Because some disease states may cause elevation of PCT levels independent of infection, it is important to consider pertinent comorbidities of the patient prior to ordering PCT labs [14–22].

While much of the current data supports PCT monitoring as a way to decrease antibiotic exposure, the clinical significance and cost efficiency of this approach have not been well elucidated at the study institution. One possible explanation for this is that the study institution already has short antimicrobial therapy durations due to a progressive antimicrobial stewardship program. Daily prospective audit and feedback by an infectious diseases pharmacist and physician is conducted on all antimicrobials prescribed at the study facility in addition to implementation of institutional policies that result in reduced use of unnecessarily broad spectrum antibiotics and excessive durations of therapy based on current evidence. As a result, many of the PCT–guided antimicrobial therapy reductions that have been demonstrated in primary literature are not shorter than minimum guideline recommended treatment, thus utility of PCT may not provide additional benefit at reducing therapy durations in a healthcare system with already short antimicrobial durations [7–14].

In November 2018, the study facility transitioned from a delayed send-out PCT test that resulted in twenty-four to seventy-two hours, with an average time of 43.9 h to a rapid in-house PCT testing modality that results within an average time of 2.4 h. The study facility allows for PCT orders at the provider's discretion, and there are no restrictions or exclusion criteria for ordering the assay. At the time of this study prescribing algorithms were not available for prescribers ordering a PCT assay, and surveillance of PCT orders for appropriateness was not a routine component of the antimicrobial stewardship program. By comparing duration of antimicrobial therapy between patients who had a send-out PCT lab ordered and an in-house PCT lab ordered, we were able to assess the utility of a quickly resulting PCT test. The aim of this study was to determine the clinical impact of in–house PCT testing on reducing antimicrobial usage.

**Aim**

This retrospective, observational review compared antibiotic durations of treatment between groups with a rapid-result versus a delayed send-out, procalcitonin test modality.

**Ethics approval**

Ethics approval was not required at the study institution prior to commencing this study, as patients and/or professionals
were not directly involved. The study was approved by the Institutional Review Board prior to commencement on August 22, 2020, reference number 20–074.

**Method**

This single-center, retrospective, pre-post cohort study was conducted at a tertiary-care community teaching hospital. Adult patients at least eighteen years of age were eligible for inclusion in the study if they had an order for a PCT lab from November 2017 to May 2020. There were 5462 PCT labs collected on 3597 patients during this time period. One hundred seventy-five patients were randomly selected from the total of 279 patients in the send-out cohort. Patients in the send-out cohort were collected from November 28, 2017 to November 27, 2018. After this time period, the study institution switched to in-house, rapid-result PCT testing and patients were eligible for inclusion in the rapid-result cohort if they had a PCT lab between November 28, 2018 and May 20, 2020. There were 175 patients randomly selected for inclusion from a total of 3334 patients identified in the rapid-result cohort. Pregnant patients were excluded. Length of antimicrobial therapy was determined by start date and time and discontinuation date and time.

Data was collected utilizing RedCap database [15]. Patient characteristics such as age, sex, and markers of illness severity such as admission to the intensive care unit (ICU) and length of stay were collected. The primary objective was to discern the impact of rapidly resulting in-house PCT testing on antimicrobial durations measured as length of therapy.

Using a risk difference estimated from previous trials, a sample size of 175 patients per arm was considered to be sufficient to estimate each individual group proportion for the primary endpoint with a precision of < 0.1 [95% confidence interval (CI)] and a power of 80%.

A statistical analysis of the data was conducted using IBM SPSS statistical software (Version 27, New York) to determine the significance of any changes seen before and after adoption of in-house, rapid-result PCT testing. Continuous parametric data was analyzed using the independent t-test. Nominal data was analyzed using the chi-square test, and continuous non-parametric data was analyzed using the Mann–Whitney U test. A p-value of less than 0.05 was considered statistically significant. Median values are reported for non-parametric data.

The primary outcome compared length of antimicrobial therapy between rapid-result PCT testing with send-out PCT testing. Secondary outcomes assessed were the incidence of *Clostridioides difficile* infection between groups, mention of PCT testing in the patients’ electronic medical record (EMR) as a reason to not initiate or de-escalate antimicrobial therapy, and the presence of comorbidities known to affect PCT levels independent of infection [1, 16–23].

**Results**

A total of 350 patients were included in the study with 175 in each group. Three patients were excluded due to pregnancy. Baseline characteristics are summarized in Table 1. There were no significant differences between groups regarding age and gender, however there was a higher incidence of renal disease and ICU admission in the rapid-result group and a greater frequency of patients admitted to a trauma service in the send-out group. Longer durations of hospital stay were observed in the rapid-result group, while the send-out group had a higher incidence of vasopressor requirement. Other serum markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were not significantly different between groups. The average number of PCT labs drawn per patient was 2.0 in the send-out group and 2.9 in the rapid-result group. The mean PCT value in the pre-intervention group was 3.96 ng/mL (range 0.01–230.68, SD 19.55). The mean PCT value in the post-intervention group was 6.76 ng/mL (range 0.01–244.41, SD 25.16). Indications for antibiotic therapy are displayed in Table 2. In the event that a patient had more than one documented infection site, the primary infectious diagnosis which prompted the initial PCT assay order was documented for the purposes of this study.

Primary outcome results are displayed in Table 3. The duration of antimicrobial treatment between the send-out and rapid-result groups was not statistically different between all patients with a median duration of treatment in the send-out group of 2.95 days compared to 3.35 in the in-house group, \( p = 0.856 \). Durations of treatment were also not significantly different when looking at subgroups of non-ICU admitted patients and ICU-admitted patients. Non-ICU patients in the send-out group had a median duration of treatment of 2.28 days and in the rapid-result cohort the median duration of treatment was 1.27 days \( (p = 0.057) \). ICU-admitted patients had a median duration of treatment of 4.04 days in the send-out group and 4.48 days in the rapid-result group \( (p = 0.877) \) (Table 3).

Secondary clinical outcomes are displayed in Table 4. PCT was rarely mentioned in the EMR as a reason to stop antimicrobial therapy with a 4% incidence in the send-out group and 9.7% in the rapid-result group. Incidence of diagnosis of *Clostridioides difficile* infection after antimicrobial therapy initiation was the same in both cohorts. Comorbidities that could interfere with the validity of PCT test results were seen in 34.9% of patients in the send-out group and 46.8% of the rapid-result group,
with renal disease being the most common comorbidity in both groups. It is notable that there was a statistically significant difference between groups in the incidence of admission for trauma and presence of renal disease. Patients in the rapid-result group were more likely to have renal insufficiency. Patients in the delayed-result group were more frequently hospitalized with traumatic injury. Incidences of additional comorbidities are displayed in Table 1. During the historic period from 2017 to 2018 practitioners at the study institution ordered 293 send-out PCT labs which resulted in $23,520 in hospital expenditures. In the year 2020 with availability of a rapid-result test modality, practitioners ordered more of these assays, 5974 in total, resulting in a hospital lab cost of $89,610.

Table 2  Documented indications for antibiotics

| Antibiotic indication (n = 350) | N (%) |
|---------------------------------|-------|
| Pneumonia                       | 169 (48.3) |
| None                            | 65 (18.5) |
| Sepsis                          | 42 (12) |
| Urinary tract infection         | 23 (6.6) |
| COPD exacerbation               | 18 (5.1) |
| Skin and skin structure infection | 13 (3.7) |
| Intra-abdominal infection       | 7 (2) |
| Fever                           | 4 (1.1) |
| Meningitis                      | 4 (1.1) |
| Bone/joint                      | 2 (0.5) |
| Fungal infection                | 2 (0.5) |
| Bacteremia                      | 1 (0.2) |

Table 3  Duration of antimicrobial treatment between the send-out and in-house cohorts

|                                | Send-out (n = 175)                      | In-house (n = 175)                       | P-value |
|--------------------------------|----------------------------------------|-----------------------------------------|---------|
| All Patients                   | Duration of treatment, days, median (IQR) | 2.95 (1.00, 5.80)                      | 3.35 (0.90, 5.98) | 0.856 |
| Non-ICU patients               | Duration of treatment, days, median (IQR) | 2.28 (0.95, 4.17)                      | 1.37 (0.40, 3.72) | 0.057 |
| ICU patients                   | Duration of treatment, days, median (IQR) | 4.04 (1.00, 7.13)                      | 4.48 (1.72, 6.50) | 0.877 |

IQR: interquartile range
The findings of this study demonstrate that availability and use of an in-house, rapidly resulting PCT assay did not reduce antimicrobial therapy durations. Baseline antimicrobial durations of therapy are short at the study institution, concordant with national guideline recommendations, due to the presence of a progressive antimicrobial stewardship program that provides recommendations on antimicrobial use for the entirety of the hospital. In contrast, many studies which have analyzed PCT utilization have suggested reductions in antimicrobial therapy days, due to the presence of a progressive antimicrobial stewardship program that provides recommendations on antimicrobial use for the entirety of the hospital. In contrast, many studies which have analyzed PCT utilization have suggested reductions in antimicrobial therapy days, due to the presence of a progressive antimicrobial stewardship program that provides recommendations on antimicrobial use for the entirety of the hospital.

While this study is limited by its retrospective nature at a single health system, it does highlight several points. First, we observed a lack of effect on reduction in durations of antimicrobial use where a robust antimicrobial stewardship program is already in place to closely monitor this. It also highlights a large percentage of inappropriately ordered PCT assays in patients with exclusions to accurate interpretation of PCT in these patients is not standardized at this institution, the lab value likely does not provide high utility in guiding antimicrobial de-escalation or discontinuation.

Cost per test was reduced by bringing PCT testing in-house, however, a substantial increase was observed in the volume of PCT test orders by providers. This resulted in increased hospital cost for number of PCT tests ordered during the study period without an observed reduction in days of antimicrobial therapy. Based on the result of this study, our institution has elected to remove PCT from the adult laboratory formulary.

Table 4 Secondary clinical outcomes

| Condition                                | Send-Out (n = 175) | In-House (n = 175) |
|------------------------------------------|-------------------|-------------------|
| PCT test mentioned in the EMR as a reason to stop therapy | 7 (4%)            | 17 (9.7%)         |
| Clostridioides difficile incidence       | 2 (1.1%)          | 2 (1.1%)          |
| Comorbidities that could interfere with the validity of PCT test result |
| Total                                   | 61 (34.9%)        | 82 (46.8%)        |
| Renal disease                          | 27 (15.4%)        | 53 (30.3%)        |
| Heart failure                           | 11 (6.3%)         | 10 (5.7%)         |
| Cardiac arrest                          | 6 (3.4%)          | 8 (4.6%)          |
| Trauma                                  | 7 (4%)            | 0                 |
| Chemotherapy                            | 2 (1.1%)          | 3 (1.7%)          |
| Cardiogenic shock                      | 0                 | 1 (0.6%)          |
| Chronic infection                       | 2 (1.1%)          | 0                 |
| Immuno compromised                      | 4 (2.3%)          | 2 (1.1%)          |
| Localized infection                     | 1 (0.6%)          | 3 (1.7%)          |
| Acute pancreatitis                      | 1 (0.6%)          | 2 (1.1%)          |

*a denotes statistical significance, p < 0.01

PCT: Procalcitonin, EMR: Electronic medical record

Discussion

Given the lack of difference in antimicrobial therapy durations observed between groups, it is evident that receipt of the laboratory value within a matter of hours does not result in a difference in use of this lab for antimicrobial decision-making in a manner that improves rates of de-escalation or discontinuation. This assessment is further validated by the scarcity with which PCT was mentioned in the patient chart as a tool utilized in clinical decision making. This conclusion does not account for non-documented clinical decision making, which cannot be studied via retrospective chart review.

In addition to lack of utility regarding rapid-result PCT labs at reducing antimicrobial durations, many of the patients who had a PCT laboratory value ordered in both the send-out and rapid-result group had a comorbidity that could lead to a noninfectious elevation of or falsely low level of PCT, 34.9% and 46.8% respectively. Because interpretation of PCT in these patients is not standardized at this institution, the lab value likely does not provide high utility in guiding antimicrobial de-escalation or discontinuation.

The study population also differed significantly between the send-out and rapid-result groups, with more critically ill patients present in the rapid-result cohort. This difference is attributed to increased provider lab orders influenced by ease of obtaining quick results with an in-house assay. By analyzing the differences between subgroups of critically ill and non-critically ill patients, investigators attempted to mitigate confounding influence of prolonged antimicrobial durations in critically ill patients compared to non-critically ill patients. An additional consideration that would provide useful knowledge towards the utility of PCT would be to collect information regarding PCT values guiding duration of antibiotics upon discharge as this endpoint was not assessed in this study.

While this study is limited by its retrospective nature at a single health system, it does highlight several points. First, we observed a lack of effect on reduction in durations of antimicrobial use where a robust antimicrobial stewardship program is already in place to closely monitor this. It also highlights a large percentage of inappropriately ordered PCT assays in patients with exclusions to accurate interpretation. Development of institutional algorithms for a guided approach to PCT ordering is an important consideration for ensuring utility only in scenarios in which evidence has demonstrated PCT aids in antimicrobial de-escalation.

Cost per test was reduced by bringing PCT testing in-house, however, a substantial increase was observed in the volume of PCT test orders by providers. This resulted in increased hospital cost for number of PCT tests ordered during the study period without an observed reduction in days of antimicrobial therapy. Based on the result of this study, our institution has elected to remove PCT from the adult laboratory formulary.
Conclusion

The results of this study indicate that in-house PCT testing that provides rapid results does not shorten antimicrobial durations when compared with send-out testing that takes multiple days to result. These findings suggest that in-house PCT is not a cost-effective tool for reducing antimicrobial durations at the study institution and financial resources may be better utilized to bolster antimicrobial stewardship efforts. In-house PCT testing may be of benefit to institutions who have average antimicrobial therapy durations that exceed guideline recommendations. Further, clinician education and implementation of institutional algorithms could serve to increase appropriate evidence-based utilization of this test.

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