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# Utility of Procalcitonin Test in Appropriate Antibacterial Choice: Retrospective Evaluation

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## ABSTRACT

***Background:*** *Procalcitonin testing (PCT) demonstrates its effectiveness for specifically diagnosing bacterial infections, as it is elevated in bacterial infections but not viral infections. Its clinical usefulness has been shown with antibiotic selection for different infections.* ***Methods:*** *This retrospective observational study aims to evaluate PCT test clinical utility in reducing the use of antibiotics, and the length of hospital stays. The study conducted at a tertiary hospital in Riyadh, Saudi Arabia included a total of 660 patients who were ordered procalcitonin test.* ***Results:*** *Subjects were grouped according to PCT level. All patients with PCT level ≥ 0.1 ng/ml (n=457) are qualified to receive antibiotic treatments. A total of 75.7% were prescribed antibiotics. The length of hospital stay (LOS) in patients who received antibiotics was statistically significantly higher than patients who did not receive any antibiotics (LOS 32.7 vs. 65.1 days, p-value=0.01). However all patients with PCT level <0.1ng/mL (n=203) show no statistically significant difference in the length of stay at hospital among patients who were prescribed an antibiotic or not (p-value=0.64). Only 31% of this group has inappropriately prescribed an antibiotic. Another infection precursor-like WBC count was also evaluated with no significant differences among groups.* ***Conclusion:*** *This study showed that the utilization of PCT guided antibiotic prescribing reduces the length of stay and reduces antibiotic use. PCT guided antibiotic prescribing can be utilized efficiently in hospital settings.*

**Keywords:** Procalcitonin, Antibiotic, Length of hospital Stay (LOS)

## INTRODUCTION

A large percentage of inpatient antimicrobial use is inappropriate which leads to drug resistance and might predispose adverse drug reactions. Approximately between 30 and 50% of antimicrobials administered to hospitalized patients may be unnecessary [1]. This trend in overprescribing antimicrobials is associated with the emergence of resistant bacteria strains. Indiscriminate use of antimicrobials increases the risk of *Clostridium difficile* infections, at the same time reduction in the use of empiric antibiotics reduces the incidence of these infections [2]. Yet, identification of the etiology of variable bacterial infections varied significantly with the lack of rapid and convenient diagnosis tools. Several biomarkers that lack specificity for infections and cross-match with sensitivity to inflammation were utilized [3]. These include fever, WBC's, C-reactive protein and procalcitonin. Procalcitonin (PCT) is quite specific and conveniently rapid biomarker but lacks sensitivity for localized infections in addition to its high cost [1,3,4].

In addition, the accuracy of the PCT tool was clearly demonstrated in a prospective observational study conducted in Syria to evaluate the usefulness of procalcitonin and other inflammatory parameters in critically ill patients specifically with sepsis. 73 patients with systemic inflammatory response and suspected infection were enrolled in this study. They found the PCT tool better than other conventional inflammatory parameters such as C-reactive protein and interleukin-6 to indicate sepsis in newly admitted patients in terms of reliability and accuracy [5]. The presence of

bacterial infection stimulates procalcitonin production through cytokines mediated stimulation (IL-1β, TNF-α). On the other hand, the cytokines produced by a viral infection like IFN-γ plays an inhibitory role for PCT production [1].

Procalcitonin plasma concentrations rise rapidly within 3-6 hours with a half-life of about 24 hours [6]. These levels correlate with the severity of illness significantly and were associated with higher mortality [7]. However, its utility as a prognostic tool or to help in infection verification suffers from many confounders that limit its utility. These confounders include physiological stress, non-bacterial cytokine activation or an unregulated PCT production. However, the tool can be of great clinical utility given the aforementioned advantages being specific to bacterial infections, its significant correlation to severity and association with mortality and it serves as a potential precursor of treatment efficacy with antimicrobials [8].

Strong evidence had shown its great utility with upper respiratory tract infections, pneumonia, COPD exacerbations, acute bronchitis as well as sepsis. PCT monitoring has been shown to decrease the duration of antibiotic exposure and antibiotic-related adverse effects in respiratory tract infections [4,9,10].

## METHODS

We conducted a retrospective chart-review study at a tertiary hospital in Riyadh, Saudi Arabia in order to study the utility of procalcitonin as a marker for upper respiratory tract infection. Data were extracted from the hospital database (BEST CARE) for all patients who have upper respiratory tract infection and ordered procalcitonin testing in the period of January 2016 to December 2017. The study proposal was approved by the Institutional review board to ensure privacy and confidentiality.

All analysis was performed by using statistical software for social sciences (SPSS). Baseline characteristics and demographic variables were compared for all patients. t-test was utilized to compare continuous variables. PCT level of 0.1 ng/ml was used to group patients for comparison. Two-tails t-test was used to compare between groups according to the outcome. A value of $p<0.05$ was considered statistically significant.

All the patients who were diagnosed with upper respiratory tract infection and ordered PCT testing were included in the study. Patients who have chronic liver disease, medullary C-cell carcinoma, any major surgery within the past 4-weeks and any autoimmune diseases were excluded.

## RESULTS

Table 1 showed the baseline characteristics for patients included in our review (n=840). There statistical analysis of baseline characteristics is presented as well for age groups and gender. All age groups comparison were statistically different, however further group-group comparison showed that only 0-18 years of age group is different than the above 50 years old group. (0-18 years *vs.* >50 years p-value=0.007) (0-18 years *vs.* 18-50 years p-value=0.21) (18-50 *vs.* >50 p-value=0.26). There were equal gender distribution and the PCT baseline comparison was statistically insignificant (p-value=0.92).

According to the inclusion and exclusion criteria, the results show that 666 (79%) of the patients are included in our analysis after exclusions that include: patients who have surgery in the past 4 weeks, chronic liver disease, c-cell carcinoma, and any autoimmune disease. A total of 486 of the included patients were taking antibiotics during the last two weeks of the PCT test result. Baseline PCT level comparison between patients who took antibiotics and patients who did not take antibiotics showed no statistical significance (p-value=0.82). A total of 174 patients (21%) were excluded as shown in Table 1.

Regarding the comorbidity, the baseline PCT results were comparison were not statistically significant. The mean PCT for diabetes mellitus patients was 2.33 ng/ml compared to the mean of 4.3 ng/ml in patients with no diabetes mellitus (p-value=0.2). Similarly, the mean PCT level for patients with hypertension was 3.0 ng/ml compared to 4.0 ng/ml in non-hypertensive patients (p-value=0.4). The mean PCT level in chronic kidney disease patients was 6.22 ng/ml compared to 3.08 ng/ ml in non-chronic kidney disease patients (p-value=0.11). Finally, the mean PCT level in heart failure patients was 5.6 ng/ml compared to 3.26 ng/ml in non-heart failure patients (p-value=0.2).

### Length of Hospital Stay (LOS) and WBC's

Patients were grouped according to the PCT level. In group with PCT >0.1 ng/ml 1: the group who received antibiotics (n=346) had an average shorter length of hospital stay (LOS) (32.7 days) compared to patients who did not receive an antibiotic (n=111) had an average longer hospital stay (LOS) (65.1 days) which was statistically significant (p-value<0.01). Thus, the utility of the appropriate use of the PCT test is 75.7%.

Similar comparison in the group with PCT<0.1 ng/ml: the group who received antibiotics (n=63), the average length of hospital stay (LOS) was (36.4 days) compared to patients who did not receive antibiotics (n=140) who had an average length of stay (41.3 days) which was statistically not significant (p-value=0.64). Thus the inappropriate antibiotic use in this group is almost 31%.

The appropriate use of antibiotics among all patient included (n=660) were 486 patients which made a 73.6% of appropriate utilization of PCT testing. This number include patients with PCT>0.1ng/ml who correctly received antibiotics (n=346) and patients with PCT <0.1ng/ml who correctly did not receive antibiotics (n=140). In group with PCT >0.1 ng/ml 1: the group who received antibiotics (n=305) had an average white B cell counts (WBC) (11.7*103/μL) compared to patients who did not receive an antibiotic (n=93) had an average white B cell counts (WBC) (11*103/μL) which was statistically not significant (p-value<0.4).

Similar comparison in group with PCT <0.1 ng/ml 1: the group who received antibiotics (n=48) had an average white B cell counts (WBC) (8.4*103/μL) compared to patients who did not receive an antibiotic (n=126) had an average white B cell counts (WBC) (9.1*103/μL) which was statistically not significant (p-value<0.35).

**Table 1 Patients' baseline characteristics**

| Characteristics | | Count | PCT Base Line Comparison (p-value) |
|---|---|---|---|
| Age (years) | 0-18 | 218/840 | 0.02 |
| | >18-50 | 183/840 | |
| | >50 | 439/840 | |
| Gender | Female | 419/840 | 0.9 |
| Inclusion | Included Patients | 660/ 840 | |
| | Excluded patients "surgery" | 58/840 | |
| | Excluded patients "Chronic Liver Disease" | 60 /840 | |
| | Excluded patients "C-Cell Carcinoma" | 12 /840 | |
| | Excluded patients "others" | 44/840 | |
| Comorbidity | Diabetes Mellitus | 237/660 | 0.2 |
| | Hypertension | 283/660 | |
| | Chronic Kidney Disease | 111/660 | |
| | Heart Failure | 95/660 | |

## DISCUSSION

The present study is a retrospective study that evaluates the decisions regarding antibiotic use in a cohort of patients with upper respiratory tract infections. The cut-off point for PCT level to grant an antibiotic prescription was 0.1ng/ml although some studies suggested higher levels [11]. Baseline characteristics of the patients in terms of age and gender were matched with no significant differences. The PCT is normally lower in the elderly age group and in certain comorbidities. All relevant comorbidities like hypertension, diabetes, chronic kidney disease, and heart failure were compared at baseline and showed no significant differences. The total number of patients who was ordered PCT was 840 patients, a total of 174 patients were excluded from our study according to the aforementioned exclusion criteria as these are not appropriate of PCT guided antibiotic decisions.

The present study shows PCT results with the level of 0.1ng/ml or more is associated with shorter length of stay if they got appropriate antibiotic treatment. However, the group with PCT less than 0.1 ng/mL shows non-statistically significant difference in the length of stay at the hospital among the group that was prescribed antibiotics or not. In a study that was done by Burkhardt, et al. that included patients with acute respiratory infections, antibiotic treatment was recommended for PCT results of > or =0.25 ng/ml. Their results suggested a possible utility of the test to decrease antibiotic use. The results were expressed as the number of days with health impairment and were not statistically significant (9.10 *vs.* 8.89; 95% CI -0.53-0.95) [11]. In our study, the length of stay was utilized as a direct outcome that reflects the appropriate use of antibiotics.

Another randomized clinical trial that was done by Briel, et al. that included 453 patients, showed a markedly significant reduction in antibiotic use with using PCT guided strategy versus standard therapy (adjusted OR, 0.01 [95% CI, 0.002-0.018]) [4]. However, this result is consistent with the results of the present study as 73.6% of the patient who were appropriately received or not the antibiotic treatment according to PCT level (>0.1 ng/ml).

A Meta-analysis (Data of two trials were used based on PRISMA-IPD guidelines) results showed that PCT guided antibiotic therapy in the primary care setting was associated with reduced antibiotic exposure in URTI patients who did the PCT test in comparison to patients who didn't do the PCT test without compromising outcomes. They found that PCT guided antibiotic therapy resulted in lower antibiotic prescription and in a 2.4 day ($p<0.001$) shorter antibiotic exposure compared to control patients [9]. Our study compares the outcome as the length of hospital stay due to infection which is of clinical value.

## CONCLUSION

White blood cells count as another clinical laboratory indicator was evaluated. There was no statistically significant difference across all patient groups. The antibiotic prescribing decision was associated with PCT elevated levels appropriately in more than two-thirds of the cases (73.6%). However, the retrospective study design might limit the accurate determination of the appropriate use of PCT testing in terms of timing and clinical decision making. The study also was performed in a single center at Riyadh that limits the total number of patients in the analysis. The results will be utilized to design a prospective study that will evaluate the utilization of PCT testing in the antibiotic regimen selection.

## DECLARATIONS

### Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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