



Procalcitonin Guided Antibiotic Management in Postoperative Cardiac Surgery Patients

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Abstract—Procalcitonin (PCT) is a biomarker for infection and its value can be obtained on the day of sampling. Prompt diagnosis of infection from other cause of physiological inflammatory responses and initiation of treatment is crucial in post cardiac surgery patients. Thus, an algorithm for PCT guided antibiotic management was developed. PCT evaluations and antibiotic usages were retrospectively studied among the patients who underwent cardiac surgery in 2012. PCT was sent when patients were clinically suspected of systemic infection. Antibiotic therapy was considered when PCT was more than 2 ng/ml. 31 patients with 33 episodes of suspected infection were evaluated by PCT. Among them, 16 patients (48%) had infections confirmed by cultures. PCT levels of patients with and without proven infection were 16.4 ± 26.5 ng/mL and 4.1 ± 10.2 ng/mL, respectively. PCT was able to predict infection with sensitivity of 81% and specificity of 82%. All patient with PCT ≥ 2 ng/ml in the true positive group were treated with antibiotics; 86% of true negative group (PCT < 2 ng/ml) avoided unnecessary antibiotic therapy. PCT guided antibiotics management can be useful for prompt initiation of antibiotics and avoidance of unnecessary treatment. This PCT guided algorithm potentially reduces hospital cost and length of stay.

Keywords —algorithm, antibiotics, cardiac surgery, diagnostics, infection, procalcitonin, sepsis

I. INTRODUCTION

Clinical signs of infection such as fever, elevated white blood cell (WBC) counts or infiltration in x-ray may occur in various conditions after major surgery. It is sometimes difficult to discern infection from other cause of physiological inflammatory responses because neither clinical findings nor

routine laboratory markers are accurate enough to diagnose infection. It is especially difficult after cardiac surgery because cardiopulmonary bypass itself is known to induce systemic inflammation [1, 2]. Procalcitonin (PCT), a serum biomarker of the systemic infection response, has been reported to be more specific than conventional markers such as WBC counts or c-reactive protein [2]. PCT is the prohormone of calcitonin but they are two distinct proteins. PCT is known to be produced mainly from extra-thyroid tissue including liver and mononuclear cells, induced by microbial toxins themselves and inflammatory humoral- or cell-mediated host response. There are numerous reports about the effectiveness of PCT assay in the diagnosis of various infections, such as community-acquired pneumonia and sepsis using cut-off of 0.5-1.0 ng/ml [3, 4]. However, its value in postoperative cardiac surgery patients remains unclear, and specific cut-off range of PCT should be established for cardiac surgery patients. We developed an algorithm for interpreting the PCT value and subsequent antibiotic management, designed for post-cardiac surgery patients. In this study, we evaluated the application and accuracy of this algorithm to guide antibiotic management.

II. METHODS

Between Jan 2012 and Jan 2013, PCT assay was ordered for patients suspected of infection in the initial post-cardiac surgery period. This data was retrospectively entered in the structured database, which was approved by the internal review board. The patients were evaluated with PCT assay if there are any clinical signs of systemic or local infection. These trigger events suggesting infection included increased WBC counts, fever of more than 101.4 F, infiltration on chest x-ray consistent with pneumonia, positive urinalysis with suspicion of uro-sepsis, increasing inotropic and vasopressor requirements after postoperative day (POD) #2 and/or wound drainage. Patients with prolonged systemic malperfusion and on immunosuppression were excluded from this study. Routine cultures (blood, sputum, urine +/- wound) were sent at the same time as the PCT assay.

In our proposed algorithm, PCT value greater than or equal to 2 ng/ml was considered to be positive; PCT value of less than 2 ng/ml was considered to be negative PCT assay (Figure 1). With clinical signs suggestive of infection, empirical broad-spectrum antibiotics (vancomycin and/or piperacillin/tazobactam) were initiated prior to the PCT level. If

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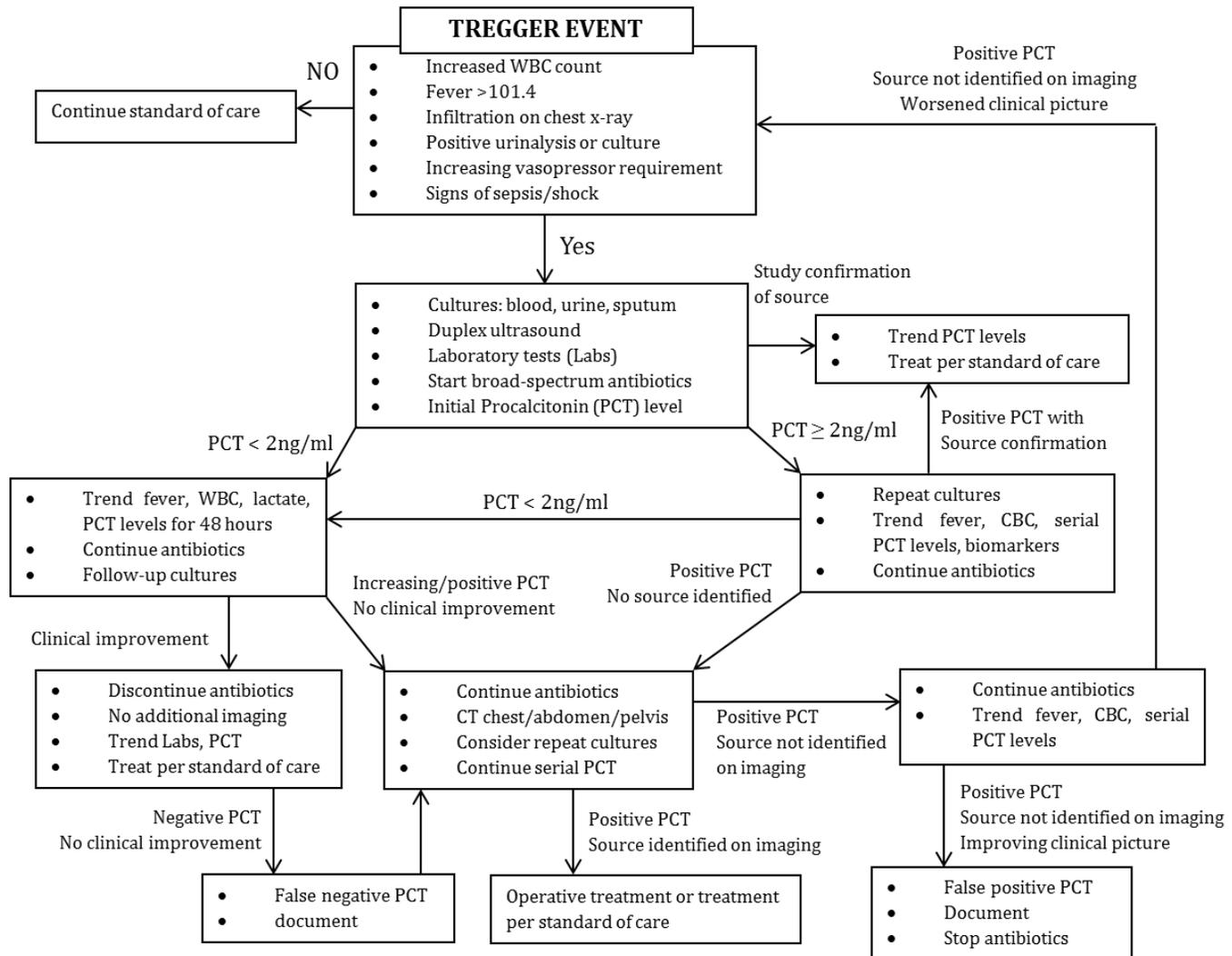


Fig. 1. Algorithmic Procalcitonin protocol for suspected infection in postoperative cardiac surgery patients. PCT: Procalcitonin, CBC: complete blood cell count, WBC: white blood cell.

the PCT value and all cultures were negative along with clinical improvement, antibiotics were discontinued within 72 hours. With a positive PCT value, empiric antibiotics were continued until specific organisms were identified by culture; in addition, PCT assays were followed until the value was less than 2 ng/ml, at which point discontinuation of antibiotics was considered in conjunction with clinical evaluation. The diagnoses of infections were based on clinical diagnoses with positive culture results. The patients evaluated with PCT were divided into 2 groups: group 1 - positive for infection and group 2 - negative for infection based on clinical diagnosis and culture results. The PCT level, temperature, WBC counts and culture results at the time of trigger events were compared between groups.

Continuous variables were expressed as mean ± standard deviation and compared with Student's t-test. Categorical variables were expressed as numbers with percentages and compared with chi-square test or Fisher's exact test as appropriate. The receiver operating characteristic (ROC) curve was plotted between PCT value and presence of infection, and

its area under the curve (AUC) was calculated. The sensitivity, specificity, and predictive values of PCT were determined by ROC to determine the best threshold for each biomarker to diagnose infection. Statistical package JMP (SAS, Cary, NC) was used for these analyses.

III. RESULTS

There were 39 patients with 41 episodes of suspected infection that were evaluated by PCT assay during this study period. 8 patients were excluded based on exclusion criteria, giving 31 patients with 33 separate episodes that were included in this retrospective study. Demographics of these 33 episodes are shown in Table 1.

Among these 33 episodes, there were 16 episodes (48%) in-group 1 of proved infection based on clinical diagnosis and positive cultures (sepsis (3), pneumonia (5), mediastinitis (3), soft tissue (2) and other infections (3)); in group 2 there were 17 episodes were negative for infection. PCT levels of patients with and without proven infection were 16.4 ± 26.5 ng/ml and 4.1 ± 10.2 ng/ml respectively (mean ± standard deviation). PCT



Table 1: Demographics of patients with or without proven infection

	All episodes	With infection	Without infection	P value
Number	33	16	17	
Age (years old)	58.2 ± 14.5	55.5 ± 13.1	61.2 ± 15.3	0.37
Male	27 (82%)	14 (88%)	13 (76%)	
Body mass index	28.8 ± 6.8	28.3 ± 7.4	29.3 ± 6.2	0.68
Procedure				
CABG	7	2	5	
Valve	11	5	8	
Other cardiac	13	9	4	
PCT (ng/ml)	10.1 ± 20.8	16.4 ± 26.5	4.1 ± 10.2	0.11
PCT ≥ 2 ng/ml	16 (48%)	13 (81%)	3 (18%)	
Temperature (F)	99.8 ± 1.5	99.4 ± 1.6	100.1 ± 1.5	0.27
WBC count (B/L)	14.9 ± 7.5	16.8 ± 9.0	13.1 ± 5.3	0.18

Data are expressed as mean ± standard deviation or number (percent).
PCT: Procalcitonin, WBC: white blood cell

levels of patients with sepsis, pneumonia and mediastinitis were 3.5 ± 2.5 ng/ml, 25.0 ± 37.0 ng/ml and 6.4 ± 7.1 ng/ml respectively. The receiver operating characteristic (ROC) curve was plotted using PCT level and whether infection was present (Figure 2). The area under the curve (AUC) was 0.864 (95% confidence interval 0.658-0.955). The AUC of the ROC between WBC and presence of infection was 0.605 (95% confidence interval 0.399-0.779). The AUC for PCT was significantly better than the AUC of WBC (p = 0.03). Table 2 shows sensitivity, specificity and predictive values of PCT with different cut-offs. When the cut-off of PCT was set to 2 ng/ml, PCT was able to predict infection with sensitivity of 81%, specificity of 82%; with the PCT at 1.5 ng/ml, sensitivity improved to 88% but specificity remained same at 82%; with the PCT at 1 ng/ml, sensitivity increased to 94% but specificity decreased to 77%. There were 15 patients with PCT ≥ 2 ng/mL and subsequent positive cultures (true positive) and 14 patients with PCT < 2 ng/mL and subsequent negative cultures (true negative).

There was 1 case of PCT value < 1 ng/ml with a positive infection; this case had mediastinitis. There were 3 cases with PCT between 1 and 2 ng/ml. Two of those were diagnosed as sepsis / pneumonia by positive culture; the other one was negative for infection.

In 3 cases, PCT was positive (> 2 ng/ml) although the cultures were negative for infection. One patient had PCT value of 2.37 ng/dl on POD#3 which decreased to 1.17 ng/ml on POD#4; infection workup was negative. Another patient was suspected of sepsis because of persistent fever, elevated WBC and prolonged vasopressor requirement with PCT of 22.29 ng/dl,

Table 2: Sensitivity, specificity and predictive values in different cut-offs of procalcitonin level.

Cut-off PCT (ng/ml)	Sensitivity	Specificity	PPV	NPV
2.0	81%	82%	81%	82%
1.5	88%	82%	82%	88%
1.0	94%	77%	79%	93%

PCT: procalcitonin, NPV: negative predictive value, PPV: positive predictive value

but all cultures remained negative. The other patient had significantly elevated PCT of 54.09 ng/ml and was treated with broad-spectrum antibiotics; PCT decreased to 17.55 ng/dl, with no positive cultures. There were no sources of infection found in these cases.

All 15 patients with PCT more than 2 ng/ml and positive for infection (true positive), were treated with antibiotics. PCT was trended until it was less than 2 ng/ml as a marker of response to antibiotics and/or for discontinuation of antibiotics in 10 of the 15 patients. Antibiotics were discontinued in 7 patients after negative PCT value and there were no recurrence of infection. Antibiotics were continued in 3 patients even after negative PCT assays; Two with mediastinitis and one with sepsis after aortic valve replacement per physician request: 12 of 14 patients (86%) with PCT below 2 ng/ml and negative for infection by culture (true negative), had empiric antibiotics discontinued by 72 hours.

IV. DISCUSSION

The diagnosis of infection after open-heart surgery is challenging for clinicians and costly to patients and hospitals. In addition to surgical trauma, cardiopulmonary bypass causes nonspecific inflammatory responses and makes the diagnosis of infection even more difficult [1, 2]. There are standard markers of infection such as fever, WBC counts and c-reactive protein, which are neither sensitive nor specific enough to diagnose infection by themselves. Cultures are usually the most specific test for diagnosis of infection, but it usually takes more than a few days for final results. PCT is a biomarker of infection and is reported to be more specific than other markers, and its value can be obtained as a point of care assay within hours after sampling. Previous studies involving PCT usefulness were mainly studied in community-acquired infections such as pneumonia and/or urinary tract infection, and among these populations the usefulness of PCT predicting infection has been established [3, 4]. The standardized cut-off of PCT was quoted 0.25 to 0.5 ng/dl in these studies. Factors other than infection can increase PCT levels, although PCT is more specific than other markers (WBC, fever etc.). For example, patients with prolonged systemic malperfusion are known to demonstrate high PCT [12]. Other conditions known to show falsely elevated PCT include burn, heat shock, severe trauma, and use of cardiopulmonary bypass [2, 13, 14]. The elevation of PCT related to the cardiopulmonary bypass is usually observed on

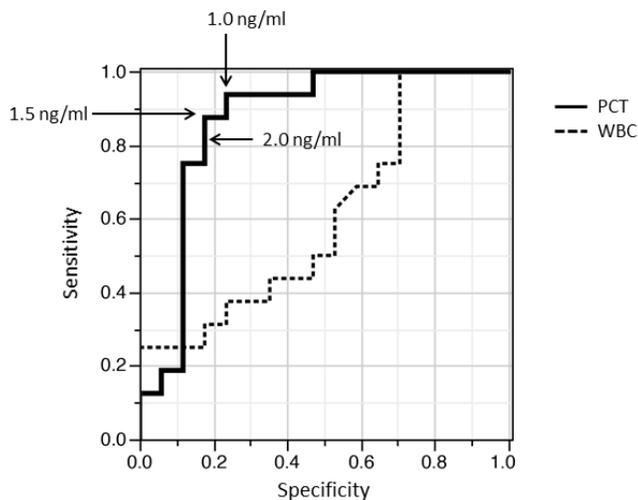


Fig. 2. Receiver operating characteristic (ROC) analysis between Procalcitonin (PCT) value and infection (solid line) and the ROC between white blood cell (WBC) count and infection (dotted line). Cut-off values are given for PCT (1.0 ng/ml, 1.5 ng/ml, 2.0 ng/ml)

POD#1 [2], and it can be explained by the fact that the half-life of PCT is 18-24 hours. Therefore, we excluded the PCT values tested on POD#1. PCT values of patients on immunosuppression have not clearly been documented. A previous study showed high PCT values with organ transplants could predict systemic infection rather than rejection [15], but PCT usefulness in immunosuppressed patients needs further research.

There have been several prospective studies utilizing PCT for the post-op cardiac surgery patient [5-11]. In several papers it was concluded that PCT was valuable for the diagnosis of infection [6, 8, 10]; other studies concluded that PCT could not discriminate between infection and non-infection but PCT was useful as a prognostic marker [9, 11]. However, applying the PCT assay protocol in these studies to actual practice would not be feasible or cost effective, because the PCT assay was done everyday in their protocol. Since the majority of the post-cardiac surgery patients do not develop postoperative infection or even concern of the infection, it is not practical to perform this assay everyday for every patient who undergoes cardiac surgery. Therefore, we sent PCT assay only for the patients with trigger events of clinical suspicion of infection.

Before we developed our PCT algorithm, PCT was assessed to correlate with clinical infections and not used for clinical decision-making. Strong positive correlation of PCT values with clinical events led us to develop the PCT algorithm. Based on our study, PCT was able to predict infection with appropriate sensitivity and specificity. The most appropriate cut-offs of positive PCT values reported in previous studies were 1-2 ng/ml for postoperative cardiac surgery. It is very difficult to universalize that cut-off value because it can change with various factors including the type of the operation, duration of cardiopulmonary bypass and the length of time from the operation [5]. Previously, Aouifi et al. showed PCT more than 1 ng/ml is suggestive of systemic infection with sensitivity of 0.85 and specificity of 0.95 in the presence of

postoperative fever [6]. They also concluded PCT more than 10 ng/ml is highly suggestive of septic shock. Similarly, Jebali et al. observed PCT value greater than 1.5 ng/ml beyond the POD#2 was strongly predictive of an infectious complication [8]. Interestingly, PCT was found to be a useful marker of the non-infectious complication after cardiac surgery. Meissner found postoperative PCT more than 2 ng/dl was high risk for any postoperative complications including infection after cardiac surgery [9]. Relatedly, Macrina et al. showed a postoperative serum PCT concentration of greater than 0.5 ng/ml is highly suggestive of a postoperative complication following coronary artery bypass surgery [10].

In our study, the cut-off of PCT was 2 ng/ml as we conducted our algorithmic protocol. Our analysis of our data demonstrated that the diagnosis of infection was improved if the PCT cut-off was 1 ng/ml, resulting in a sensitivity of 94%. There was only one case with PCT below 1 ng/ml in infection group; this was a contained sternal abscess. PCT values have been reported to be low in case of contained infection and abscess, and it could be the limitation of the PCT assay [6]. Contained or space infections generally are identified by physical examination or imaging study, and the treatment would be focused on drainage rather than systemic antibiotics use. When PCT in our study was less than 1 ng/ml, infection was excluded with a negative predictive value of 93%. However, clinicians should know there is a ~ <8-10% risk of localized infection or abscess, and careful examination and imaging study may be helpful to minimize the false negative PCT assay. When PCT value was greater than 2 ng/ml, the possibility of infection was high with positive predictive value of 81%. Cultures should be sent and empirical antibiotics are strongly recommended until all cultures are reported at 72 hours. With borderline PCT value between 1 and 2 ng/ml, we recommend routine cultures and antibiotics; especially given two of three episodes had severe systemic infection in our study. Once antibiotics were started based on PCT level, PCT should be trended for evaluation of response to the antibiotics treatment.

Trending of PCT values has been shown to correlate with severity of infection and was useful to judge whether treatment is effective [3]. Moreover, it provides useful information for the timing to discontinue antibiotics. The PCT level to discontinue antibiotics recommended for community acquired pneumonia is 0.25 ng/ml, which is the value initiation of antibiotics is recommended [4]. Therefore PCT less than 1 ng/ml would be safe to discontinue antibiotics in post-operative cardiac surgery patients. In our study, antibiotics were discontinued when PCT was less than 1 to 2 ng/ml or there was a 50% decrease in value on 2 consecutive days from the initial PCT value, and there was no clinical evidence of infection. Employing our PCT based algorithm, the use of unnecessary treatments would be avoided and antibiotics could be discontinued with appropriate timing. Therefore, this algorithm potentially reduces the hospital cost and shortens the length of stay.

The limitation of this study includes its retrospective design, small sample size, and the diagnosis of infection. In this study, the diagnosis of infection was based on clinical diagnosis



concomitant with positive culture results. All cultures were sent before antibiotics were started; depending on the bacterial loads, routine cultures may not be sensitive enough for all infections. We used a positive culture as a requirement to be included in the infection group in order to maintain objectivity.

V. CONCLUSIONS

PCT assays incorporated in the algorithm for suspected infection was able to predict infection with good sensitivity and specificity in postoperative cardiac surgery patients. Baseline PCT values can vary depending on post-op timing or other conditions; however, PCT cut-off value of 1 to 2 ng/ml appears to be best practice guideline for suspicion of infection. This PCT based algorithm potentially reduces hospital cost and length of stay. A prospective study comparing this algorithmic protocol with and without PCT is required for further verification of this study to evaluate antibiotic stewardship, cost and adherences to algorithm guided management.

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