Utility of Procalcitonin in the Management of Hospital-Acquired Pneumonia - A Review

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Abstract: Procalcitonin was introduced to management of hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA), in its 2005 HAP guidelines. It was based on the assumption that positive procalcitonin (PCT) results indicative of HAP/VAP of bacterial aetiology will prompt antibiotic therapy, and improve clinical outcomes. Antibiotic stewardship by monitoring of PCT kinetics resulted in shorter antibiotic treatment durations with early cessation of therapies. The diagnostic part is no more recommended due to weak evidence from studies. Beyond diagnostic uses, some studies have shown that positive PCT levels are associated with poorer clinical outcomes in HAP/VAP, Healthcare-associated pneumonia and community-acquired pneumonia. The article will discuss the diagnostic role briefly and mainly the role as a prognostic indicator in the management of HAP/VAP.

Keywords: Hospital acquired, mortality, pneumonia, procalcitonin, respiratory tract infection, ventilator associated pneumonia.

1. INTRODUCTION

Hospital-acquired pneumonia (HAP) is the most common life-threatening hospital-acquired infection, and the majority of cases are associated with mechanical ventilation. Hospital-acquired pneumonia is associated with significant increases in length of hospital stay, mortality, and costs [1]. Hospital-acquired pneumonia, including Healthcare-associated pneumonia (HCAP), remains the most commonly reported infection (157,700 cases — out of total 721,800 cases of nosocomial infection) in the USA in the year 2014 [2]. To prevent irrational overuse of antibiotics, the role of the biomarkers like procalcitonin (PCT) C-reactive protein was suggested to estimate the presence of sepsis and response to antibiotics [3, 4]. In addition to clinical signs and symptoms, blood markers may assist in patient monitoring [5-8].

Procalcitonin was described as a marker of sepsis in 1993 [9]. PCT is a host-response marker that is up-regulated by microbial toxins, and specific pro-inflammatory mediators (e.g., Interleukin -1b, Tumour necrosis factor-α, Interleukin-6) and is down regulated during recovery [10]. The expression of PCT is attenuated by the cytokines typically released in response to a viral infection (e.g., Interferon-γ); thus an elevated PCT is usually indicative of a bacterial infection. The induction of PCT is more strictly regulated as compared to cytokines: there is no significant PCT production in stimulated whole blood, but PCT production has been observed in various tissues during sepsis.

The induction of circulating PCT is related to the activation and adherence of monocyte cells, and is typically seen during sepsis as well as less frequently in other conditions, such as after tissue trauma [11], sterile inflammation or viral infection [4]. Varieties of human tissues express PCT-I, PCT-II, and CGRP-1 mRNAs, with highest levels detected in liver, testis, lung, prostate, kidney, and small intestine, differing in the proportions of expression [12]. Although PCT is constitutively secreted by C cells of the thyroid gland and K cells of the lung, PCT detectable in plasma during inflammation is not produced in C-cells of the thyroid, and the probable site of PCT production during inflammation is the neuroendocrine cells in the lungs and intestine [13].

Procalcitonin has been previously demonstrated to be helpful in antibiotic stewardship decisions [14-16]. The underlying assumption was that serum PCT results indicative of HAP/VAP of bacterial aetiology, will prompt antibiotic therapy, improving clinical outcomes. Although American Thoracic Society/Infectious Disease Society of America in its 2005 guidelines suggested no role of Procalcitonin for diagnostic purposes or in antibiotic duration [17], but, the recent ATS/IDSA guidelines have not recommended PCT testing for diagnostic purposes, and the role of biomarkers in the management of HAP has become almost obsolete [18]. In addition to its diagnostic value, there is a growing evidence, suggesting the role of PCT in predicting poorer clinical outcome and mortality in patients with lower respiratory infections [19, 20]. The PCT kinetics have also been shown to predict mortality and treatment failure in sepsis [21-27].
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In this review article, we reviewed various roles of PCT in the management of HAP (Excluding CAP), emphasising on the utility of PCT as a predictor of mortality, in particular.

2. REVIEW

We selectively searched studies using PubMed, Cochrane and Web of knowledge library. The search items were as follows: (procalcitonin or PCT), (Hospital-acquired pneumonia or HAP), Healthcare-associated pneumonia or HCAP) and (mortality or prognosis). Reference list of selected articles was also carefully reviewed, to obtain relevant articles. Eligible studies had to have used ATS definition of HAP/HCAP [17], and must have used PCT as a biomarker to predict treatment outcome, regarding mortality.

3. DIAGNOSTIC ROLE AND ANTIBIOTIC TAILORING OF PCT IN HAP

The underlying assumption was that serum PCT results indicative of hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) of bacterial aetiology, will prompt antibiotic therapy, and improve clinical outcomes. However, the cut-offs used to distinguish patients who had HAP/VAP from those who did not vary from 0.5 - 3.9 ng/mL, and none of the cut-offs used in the studies was subsequently validated.

Hence, the recent ATS/IDSA guidelines have not recommended PCT testing for diagnostic purposes in HAP [18]. The ATS/IDSA panel pooled the performance characteristics of serum PCT for the diagnosis of HAP/VAP via a meta-analysis using a bivariate regression approach, using six studies [28-33]. The panel found that for diagnosing HAP/VAP, PCT demonstrated the sensitivity of 67% (95% CI, 53%-79%), and specificity of 83% (95% CI, 43%-97%). The calculated positive likelihood ratio, negative likelihood ratio, and diagnostic Odds ratio were 3.9 (95% CI, 9.17-5), 0.4 (95% CI, 25-62) and 10 (95% CI, 2-49), respectively, indicating moderate overall test accuracy. The source studies also had the severe risk of multifactorial bias, further affecting the ATS/IDSA recommendations. 18 NICE guidelines for management of pneumonia in adults (December 2014) also didn’t include PCT in management [34].

In the year 2012, Cochrane acute respiratory infections group in its review of procalcitonin to initiate or discontinue antibiotics in acute respiratory infections (ARI), which included 14 trials and 4221 participants, concluded that the use of PCT was not associated with higher mortality rates or treatment failure. There were 118 deaths (5.7%) of 2085 patients assigned to PCT groups as compared to 134 deaths (6.3%) in 2126 control patients (adjusted OR 0.94, 95% CI 0.71-1.23). Treatment failure occurred in 398 procalcitonin group patients (19.1%) and 466 control patients (21.9%). PCT guidance was not found to be associated with increased mortality or treatment failure in any clinical setting, or ARI diagnosis. There was a significant reduction in total antibiotic exposure [median (interquartile range)] from 8 (5-12) to 4(0-8) days; adjusted difference in days, -3.47, 95% CI -3.78 to -3.17, and across all the different clinical settings and diagnoses. The review group emphasized the need for high-quality research to confirm the safety of this approach for non-European countries and patients in intensive care. There is also need to establish cost-effectiveness by considering country-specific costs of PCT measurement and potential savings in consumption of antibiotics and other healthcare resources, as well as secondary cost savings due to lower risk of side effects and reduced antimicrobial resistance [35].

As per 2016 ATS/IDSA HAP guidelines, among all the biomarkers, the only biomarker to have any role in the management of patients with HAP is PCT in combination with clinical criteria, in determining the length of treatment [18].

4. PROCALCITONIN AS A PROGNOSTIC INDICATOR IN HAP

Several studies have shown PCT to be useful as a prognostic indicator in patients with pneumonia. The studies were predominantly conducted among patients with community-acquired pneumonia (CAP) [19, 36-48], healthcare-associated pneumonia (HCAP) [20, 48, 49] and HAP/VAP [31, 32, 50-56]. In the most recently published study, Hong DY et al. [20] used PCT in HCAP patients to determine its efficacy as an indicator for predicting mortality. The study concluded that high PCT (>2 ng/ml) on admission was strongly associated with ICU admission (OR 3.734, 95%CI 1.753-7.951; p=0.001) and 30-day mortality (HR 2.549,95% CI 1.250-5.340; p=0.035). 12 The ROC analysis of PCT was suggestive of fair discrimination power regarding 30-day mortality in HCAP patients (0.768 of the AUC). Another study was done by Mc Cluskey et al., in which 317 patients of CAP and HCAP were included. The study found that for the total population at PCT values of 0.1, 0.25, and 0.5 ng/mL, sensitivity was 63%, 54%, and 46%, respectively, for the composite endpoint, all with negative predictive value >80%. The specificity of PCT-based prognosis using these cut-offs was highest when evaluating the HCAP subpopulation, whereas sensitivity was highest in the CAP group [48].

Details of studies done in evaluating the utility of PCT in predicting the more inferior treatment outcome, in cases of HAP/VAP are given in Table 1.

As HCAP is no more included in HAP group, and there is only one study done exclusively for HCAP, the studies can be broadly grouped into CAP and VAP.

Among some studies on the utility of PCT in CAP, Andrijevic et al., in a recently published study, found PCT to be useful in predicting mortality in cases of community-acquired pneumonia. ROC curve analysis confirmed significant role of PCT in predicting mortality among patients with CAP (AUC ± SE = 0.667 ± 0.062; 95% CI -0.546-0.789; p=0.012), with the sensitivity of 76% and specificity of 61.8% at a cut-off value of 2.56 ng/mL [38]. Kasamatsu et al., in a similar study in CAP patients, found 30-day mortality among patients with higher PCT (>0.5 ng/ml) was significantly higher (12%) [19]. Bloos et al., also reported that PCT was associated with severity of illness and was comparable to APACHE II score, as a prognostic marker of adverse treatment outcomes [57].
We could not find any study where the role of PCT has been evaluated for non-ventilator associated HAP. Majority of the studies were conducted in cases of VAP. A single measurement of Procalcitonin has been found to be an essential tool to identify patients at risk of adverse outcomes, even in a non-sepsis situation, as was observed by Klingele et al., in their study of 751 patients undergoing elective cardiac surgery. A single PCT level was taken within 24 hours after surgery, which was able to predict patients at higher risk of delayed complications [58].

In a most recent (May 2017), large, multicentre, blinded, prospective observational clinical trial - Multicentre Procalcitonin Monitoring Sepsis (MOSES) study, it was found that failure to achieve more than 80% reduction in PCT levels, is a significant independent predictor of mortality and may aid in sepsis care [59]. The data from 107 non-survivors and 539 survivors were analyzed, for the primary endpoint of 28-day all-cause mortality. Among the non-survivors, confirmed infection was found in 82% of cases, with initial median PCT of 5 [Interquartile range=1-21.9]. The emphasis was on PCT kinetics from baseline to day 4. A decrease of more than 80% was seen in 22% of non-survivors, compared to 70% where a reduction in PCT kinetics was less than or equal to 80%. Prognostic role at these cut-offs showed a sensitivity of 77% (95% CI 69-85%) with a specificity of 39% (95% CI 36-43%). Mortality was also found to be higher in patients still hospitalised in ICU at day 4 (26%). Mortality was three-fold increased, among patients with high baseline PCT value >2μg/L, in which PCT did not drop by >80% (19% vs 5%). For patients in ICU at day 4, low baseline PCT of <2μg/L, mortality was about three-fold higher if PCT did not drop by >80% compared with PCT that decreased by >80% (26% vs 10%) [59].

Also, the meta-analysis of 3 randomized control trials [60-62], by ATS/IDSA panel, which specifically evaluated the discontinuation of antibiotic therapy for VAP on the basis of PCT levels plus clinical criteria vs clinical criteria alone, it was found that, the former group had a shorter duration of antibiotic therapy (9.1 days’ vs 12.1 days; p<0.00001, but no difference in mortality. Other outcomes included no effects on the duration of mechanical ventilation, length of ICU stay, length of hospital stay, the incidence of recurrent pneumonia, or development of resistance [18].

The cost-effectiveness of serial PCT monitoring, is a big challenge, especially in the setting of developing nations. The economics of PCT compared to the economics of antibiotics needs to be considered. The PCT testing cost in India ranges from 1000 - 2800 INR, across various centres.

Table 1. Comparison of various studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Clinical Setting</th>
<th>Endpoint</th>
<th>Assay</th>
<th>Sample Size</th>
<th>Prevalence %</th>
<th>Pneumonia Type</th>
<th>Cut Off (ng/mL)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilas et al.</td>
<td>2010</td>
<td>PR+ CR.</td>
<td>ICU</td>
<td>28-day mortality</td>
<td>PCT-LIA</td>
<td>45</td>
<td>35.60%</td>
<td>VAP</td>
<td>0.42</td>
<td>87.5</td>
<td>65.5</td>
</tr>
<tr>
<td>Su et al.</td>
<td>2012</td>
<td>PR</td>
<td>ICU</td>
<td>28-day mortality</td>
<td>VIDAS</td>
<td>32</td>
<td>56</td>
<td>VAP</td>
<td>9.47</td>
<td>66.7</td>
<td>90.9</td>
</tr>
<tr>
<td>Seligman et al.</td>
<td>2011</td>
<td>PR+ CR.</td>
<td>ICU</td>
<td>28-day mortality</td>
<td>LUMItest PCT</td>
<td>71</td>
<td>36.6</td>
<td>VAP</td>
<td>0.74</td>
<td>84.6</td>
<td>57.8</td>
</tr>
<tr>
<td>Duflo et al.</td>
<td>2002</td>
<td>PR+ CR.</td>
<td>ICU</td>
<td>Mortality</td>
<td>LUMItest PCT</td>
<td>44</td>
<td>64</td>
<td>VAP</td>
<td>2.6</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Lyut et al.</td>
<td>2005</td>
<td>PR+ CR.</td>
<td>ICU</td>
<td>Adverse outcomes</td>
<td>Kryptor PCT</td>
<td>76</td>
<td>61.8</td>
<td>VAP</td>
<td>1</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>Zelinska et al.</td>
<td>2012</td>
<td>PR</td>
<td>ICU</td>
<td>Mortality</td>
<td>Kryptor PCT</td>
<td>34</td>
<td>21</td>
<td>VAP</td>
<td>0.62</td>
<td>100</td>
<td>66.3</td>
</tr>
<tr>
<td>Savva et al.</td>
<td>2011</td>
<td>MPR+CR</td>
<td>ICU</td>
<td>28-day mortality</td>
<td>Kryptor PCT</td>
<td>180</td>
<td>38.5</td>
<td>VAP</td>
<td>0.92</td>
<td>80</td>
<td>88.5</td>
</tr>
<tr>
<td>Porfyridis et al.</td>
<td>2014</td>
<td>PR</td>
<td>Ward</td>
<td>Hospital mortality</td>
<td>Kryptor PCT</td>
<td>58</td>
<td>17.2</td>
<td>HAP</td>
<td>1.1</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>Tanriverdi et al.</td>
<td>2015</td>
<td>PR</td>
<td>ICU</td>
<td>Mortality</td>
<td>Kryptor PCT</td>
<td>45</td>
<td>48.8</td>
<td>VAP</td>
<td>1</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>Bloos et al.</td>
<td>2011</td>
<td>PR + CR</td>
<td>ICU</td>
<td>28-day mortality</td>
<td>LUMItest PCT</td>
<td>175</td>
<td>18.3%</td>
<td>CAP, HAP, VAP</td>
<td>1.1</td>
<td>OR 7 (95%CI 2.6-25.2)</td>
<td></td>
</tr>
<tr>
<td>Hong et al.</td>
<td>2016</td>
<td>PR+CR</td>
<td>Ward &amp; ICU</td>
<td>30-day mortality</td>
<td>Electrochemiluminescence Immunoassay</td>
<td>245</td>
<td>18</td>
<td>HCAP</td>
<td>0.81</td>
<td>77.3</td>
<td>67.7</td>
</tr>
</tbody>
</table>
Also, the data on HAP is scarce, and studies on PCT from developing nations, like India is lacking.

PCT Kinetics despite showing usefulness in the management of sepsis, by predicting the adverse treatment outcome, the prognostic role of PCT in HAP/VAP has not been addressed in recent ATS/IDSA HAP guidelines. ATS/IDSA panel in its 2016 HAP guidelines have not mentioned any diagnostic or prognostic role of PCT, and the only purpose is in determining the duration of antibiotic therapy, in combination with clinical criteria. The panel has also suggested that the decreased antibiotic exposure almost certainly reduces antibiotic costs and possible side effects, but PCT testing is more costly and burdensome than clinical criteria alone. There is a concern regarding the possibility of falsely low PCT levels encouraging inappropriate discontinuation of necessary antibiotic therapy, and falsely high PCT levels leading to the continuation of unnecessary antibiotic treatment [18].

5. LIMITATIONS

The studies included in review vary in patient selection, cut-off selection, and statistical test applied. Meta-analysis was not done and no Forest-plots were made, because of statistical inconsistencies among various studies and very few studies having measured hazard ratio.

CONCLUSION

There is need to develop study models (blinded, randomised), using standard PCT cut-offs, involving non-ventilator associated pneumonia, as most of our understanding of HAP comes only from VAP. Also, the implications in the context of developing nations need to be studied.

PCT use in the management of HAP is no more recommended for diagnostic purposes. PCT and PCT kinetics using serial readings is a fair predictor of poor treatment outcome and in-hospital mortality, especially in VAP. Also, using PCT with clinical parameters can also decrease the antibiotics exposure, unwanted side effects and cost of treatment and length of treatment.

ABBREVIATIONS

ATS/IDSA = American Thoracic Society/Infectious Disease Society of America
CAP = Community Acquired Pneumonia
CI = Confidence Interval
HAP = Hospital-Acquired Pneumonia
HCAP = Healthcare-Associated Pneumonia
PCT = Procalcitonin
VAP = Ventilator Associated Pneumonia

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

Kumar et al.


