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The role of procalcitonin in the management of pleural infection.

Duneesha de Fonseka[1], Nick A Maskell[1].

Author affiliations:

[1] Academic Respiratory Unit, University of Bristol, Southmead Hospital, Bristol, UK

Corresponding author:

Dr Duneesha de Fonseka

Level 2, Learning Research Building, Southmead Hospital, Bristol, UK

duneesha@gmail.com

07779268062

Abstract:

Purpose of review

Pleural infection is a common problem associated with significant morbidity and mortality. Systemic or pleural fluid markers for reliably identifying pleural infection is limited. Procalcitonin is known to be elevated in bacterial infection and is currently used for diagnosis and decision making regarding antibiotic duration in respiratory infections. This review investigates if there is a role for serum and pleural fluid procalcitonin in diagnosis and management of pleural infection.

Recent findings:

Studies investigating the role of procalcitonin have been limited by small patient numbers and heterogenous control populations. Overall, serum PCT does not have a role superior to that of CRP or leukocyte count in diagnosing pleural infection or monitoring response to treatment. Similarly, pleural fluid procalcitonin demonstrated low sensitivity and specificity for diagnosing pleural infection. There was no role for PCT in determining which patients would require surgery as opposed to tube drainage alone.

Summary:

There is currently insufficient evidence to recommend routine use of procalcitonin for diagnosis and monitoring of pleural infection.

Keywords:
Pleural infection; procalcitonin; empyema

Introduction:

Pleural infection is a common disease with a combined annual incidence of up to 80,000 in the UK and USA [1], with up to 30% of patients requiring thoracic surgery, or dying as a consequence of the infection [2]. Therefore, rapid diagnosis, optimum management and escalation of therapy is essential.

Current methods of diagnosis of pleural infection largely relies upon biochemical investigations such as a low pleural fluid pH/glucose (in the correct clinical setting), drainage of pus from the pleural cavity or microbiological growth of an organism on culture [3]. Radiological imaging such as thoracic ultrasound or CT may suggest the presence of pleural infection however, confirmation is required by means of above investigations. Systemic markers of infection such as total leukocyte count (LCC) and C-reactive protein (CRP) are relied upon for monitoring response to treatment and to guide further management [3]. However, these markers are not specific for infection, they can often be raised in other systemic inflammatory conditions and viral infections. Therefore, a marker selective for pleural infection that can be relied upon to guide management has been a topic of interest for clinicians and researchers.

Procalcitonin (PCT) is a 13 kDa protein secreted by the thyroid gland as a precursor to calcitonin [4]. Normal PCT level is undetectable in blood at levels <0.1 ng/ml [5]. Sepsis, infection or duress from other injury has been shown to elevate the levels of PCT in the blood, peaking at about 2-6 hours from insult and remain elevated for > 24 hours, due to its half-life of 20-24 hours [4-6]. An increasing body of evidence supports the use of PCT for guiding treatment in acute respiratory infections [7] and other bacterial infections associated with critical care admission [8, 9]. However, in certain conditions such as atypical pneumonia, tuberculosis and ventilator associated pneumonia the reviews on the performance of PCT as a diagnostic marker is mixed[10]. The role of PCT in pleural infection remains unclear with a number of trials showing conflicting results hence the need for this review.

Serum Procalcitonin for the diagnosis of pleural infection

One of the earliest studies to investigate the role of serum PCT (s-PCT) in pleural effusions was conducted by Lin et al [11] in a cohort of 82 patients; 45 para-pneumonic effusions (PPE) and 37 non-PPE. In this study they measured both serum and pleural fluid PCT (pf-PCT) to evaluate their diagnostic role. PPE patients were sub-grouped as simple PPE (no organisms were found on culture or Gram stain), complicated PPE (LDH>1000 units/L; glucose < 40mg/dL; or pH < 7.2) or empyema (frank pus). They discovered both s-PCT and pf-PCT to be higher in the PPE group compared to the non-PPE group. A significant difference (p=0.0003) was seen between the median s-PCT levels of 0.34 vs 0.1 ng/mL for PPE vs non-PPE groups respectively. Interestingly, within the PPE sub-groups the greatest median value was seen in the simple PPE group with a level of 1.37ng/ml, followed by complex-PPE 0.67ng/ml and empyema with a median s-PCT of 0.24 ng/ml. This irregularity could perhaps be explained by their definition of PPE 'an effusion associated with community acquired pneumonia'. Some of the increase in the s-PCT can therefore be due to the acute systemic infection relating to pneumonia. Hence the very high levels of s-PCT seen in the simple PPE group.

One of the largest studies to investigate the role of serum PCT in diagnosing pleural infection was conducted by Dixon et al [12]* in a cohort of 425 consecutive patients with a unilateral effusion, seen at a single centre over a 5-year period. In this study the authors aimed to investigate if serum PCT can be superior to CRP and LCC. Of the 425 patients included in the final analysis, 80 patients had a diagnosis of pleural infection. The median serum PCT level for the pleural infection cohort was 0.2 ug/L, while pleural TB patients (n=10) had a median PCT of 0.1 ug/L renal failure patients (n=6) had a median PCT of 0.1 ug/L. The control group in this study included pleural effusions of a variety of causes, including malignancy, inflammatory pleuritis, pleural tuberculosis, cardiac and renal failure. Receiver operating curve (ROC) analysis demonstrated that at an optimum cut-off of 0.085 ng/ml PCT had a sensitivity of 69% and a specificity of 80% for diagnosing pleural infection, which was no superior to that of LCC and CRP, sensitivities of 69% and 88% with specificities of 80% and 67%, respectively. They

were also able to demonstrate that the baseline PCT did not show greater prognostic ability than LCC or CRP when identifying patients who would require thoracic surgery.

These findings have been mirrored in other small studies. An earlier study by Ko et al [13] attempted to evaluate the performance of both serum and pleural fluid PCT in patients with PPE. In their study of 25 bacterial PPE (confirmed by isolation of microorganism in pleural fluid, blood or bronchoalveolar lavage quantitative culture), 16 non-bacterial pleural effusions and 9 control patients, the median serum PCT was 0.136, 0.081 and 0.085 ng/mL, respectively (p=0.205). Although the median s-PCT was higher in the pleural infection group, this did not meet statistical significance to support a role for s-PCT in diagnosing pleural infection. This may be due to the small number of participants in the pleural infection group.

A retrospective study by He et al [14] investigated the role of s-PCT in diagnosing PPE in 148 patients admitted with pleural effusions. They reported that s-PCT levels were significantly elevated in patients with PPE (n= 47) as opposed to malignant pleural effusions (n=46), tuberculous pleural effusions (n=41) and transudative effusions (n=14); s-PCT levels of 5.44ng/ml, 0.15 ng/ml, 0.18 ng/ml and 0.09 ng/ml respectively. This study was able to demonstrate a potential role for s-PCT in discriminating pleural infection from other causes of an effusion but had a number of study limitations. Firstly, it did not examine whether s-PCT had a superior role to that of LCC or CRP for diagnosing infection. Secondly, it did not explore the role of PCT in determining which patients would require tube drainage or surgery. Finally, the authors did not separate the subtypes of PPEs such as simple PPE, complex PPE or empyema. As management of the different types of PPE is different, it would have been useful to investigate the role of serum PCT in different subgroups.

Similarly, a study by El-Shimy et al [5] comparing 4 groups of pleural effusions found comparable results to the above studies. They were able to demonstrate a higher mean s-PCT of 2.171 ng/ml for PPE (n=14) compared to the other 3 causes of effusions transudative effusions (n=8), tuberculous pleural effusions (n=14) and malignant pleural effusions (n=18). Interestingly the malignant cohort in

this study had a higher mean serum PCT of 0.965 ng/ml, yet the difference in mean PCT levels were statistically significant; $p<0.001$. It should be noted this study only included simple parapneumonic effusions with no evidence of active pleural infection. They attributed the raised s-PCT to increased systemic inflammation.

How much of the raised serum PCT is attributable to infection or inflammation is another question of interest. A proof of principle study by McCann et al [15] investigated s-PCT levels in 3 cohorts of patients; pleural infection as confirmed by Multicentre Intrapleural Sepsis Trial (MIST) criteria [2, 16], malignant pleural effusion cohort, and patients who underwent Talc pleurodesis as a part of another trial. The authors compared serum PCT levels in 32 pleural infection patients, with a matched control population comprising of malignant pleural effusions. There was a significant difference in the median PCT levels between the 2 groups (0.58ug/L vs 0.34ug/L; $p = 0.003$). On evaluation of the s-PCT levels in 32 patients undergoing Talc pleurodesis - where intense iatrogenic pleural inflammation is induced for the management of pleural fluid - the rise in serum PCT was only minimal before and after the procedure. Interestingly, CRP in the same setting increased by 3.6-fold. Although the numbers are small, this study was able to demonstrate that the PCT level remains fairly stable in an intense pleural inflammatory reaction such as pleurodesis. This study was also unable to show a role for PCT in predicting which patients would require surgery or would die from the infection, compared to those who would do well with conservative management.

<u>Pleural fluid Procalcitonin for the diagnosis of pleural infection</u>

A study by Porcel et al in 2009 set out to investigate a number of inflammatory markers including PCT in pleural fluid for discrimination between infectious complex PPE and other causes of pleural effusions [17]*. In this study of 308 patients, 50 patients had tuberculous pleurisy, 60 patients had an uncomplicated parapneumonic pleural effusion, 68 had a complex parapneumonic pleural effusion and 30 had empyema. Transudates, malignant pleural effusions and miscellaneous causes made up the rest of the control population. The median pf-PCT for the empyema group was 0.19 ng/ml,

complex PPE 0.26 ng/ml. Of note, the miscellaneous group had a median pf-PCT of 0.33 ng/ml, the highest in this cohort of 308 patients. The miscellaneous cohort included a variety of pathologies including post-traumatic effusions, pulmonary emboli related effusions, abdominal abscesses and post-coronary artery bypass surgery patients. In this study pf-PCT failed to discriminate between different types of infectious and non-infectious causes for pleural effusions. However, given the pf-PCT levels it is worth considering whether some of the s-PCT could be leaking into the pleural fluid causing falsely high levels in this sub-group, particularly those with other infectious aetiologies. At a cut-off of 0.25 ng/ml pf-PCT was 45% sensitive and 72% specific for diagnosis of an infectious effusion.

Two studies mentioned above examined both serum and pleural fluid PCT for its diagnostic role. The study by Ko et al [13] reported a significant difference ($p<0.001$) in the pf-PCT between bacterial (0.24 ng/mL), non-bacterial (0.09 ng/mL) and control groups (0.08 ng/mL). Using a receiver operating curve (ROC) analysis they were able to demonstrate a sensitivity of 80% and a specificity of 76%, at a cut-off of 0.17 ng/mL. Lin et al [11] reported PPE versus non-PPE median pf-PCT levels at baseline of 0.37 vs 0.08 ng/mL, respectively ($p=0.01$). In PPE sub-groups, the simple PPEs had the most elevated pf-PCT level at 0.43 ng/ml, while empyema pf-PCT 0.18 ng/ml and complicated PPE pf-PCT was at 0.2 ng/ml. At a cut-off of 0.18 ng/ml, pf-PCT had a sensitivity of 66.7% and specificity of 77.4%. Although the numbers are small in both studies, they show promising results for a potential role of pf-PCT in discriminating PPE from non-PPE.

A more recent study by Khosla et al [18] investigated the utility of pf-PCT in discriminating infectious from non-infectious pleural effusions. In this study of 75 patients the diagnostic criteria for pleural infection were pleural fluid Gram stain or culture positivity, presence of pus or the presence of an effusion accompanied by clinical features and radiographic evidence of lung infiltrate, to define infectious pleural effusions. Eighteen patients had an infectious pleural effusion by these criteria. The study demonstrated a significant relationship between pf-PCT in infectious and non-infectious pleural effusions; median pf-PCT 1.088 versus 0.123 for infectious versus non-infectious respectively. At a cut-

off of 0.25 ng/ml pf-PCT had a sensitivity of 77.8% and specificity of 74.1%, for diagnosing an infectious pleural effusion. Interestingly, the median fluid pH for the infectious group was 7.37 and non-infectious group 7.40 (p=0.11). Similarly, the median glucose level was 126 mg/dL and 106 mg/dL respectively, lower in the non-infectious group, calling into question the diagnostic criteria used to classify pleural effusions as infectious. This study was a small study with 18 patients in the infectious group, some of whom were not diagnosed according to the commonly used criteria for pleural infection, which may explain the differences in the pleural fluid pH and glucose levels.

A meta-analysis by He et al [14] reviewed the literature relating to procalcitonin in a parapneumonic setting in both serum and pleural fluid. They analysed 11 studies involving 1320 subjects, of whom 463 were PPE patients and 857 were controls. The summary characteristics from the pooled analysis showed a sensitivity and specificity of 78% and 74% for s-PCT for diagnosing PPE. Pleural fluid PCT performed slightly worse with a sensitivity of 62% and specificity of 71% for detecting parapneumonic effusions. The summary ROC curves showed an are under the curve of 0.84 for s-PCT and 0.80 for pf-PCT suggesting good overall performance of s-PCT. Different studies analysed in this meta-analysis used different cut-off levels for both serum and pleural fluid, and different cohorts for controls (benign, malignant, transudative) which may affect the quality of the meta-analysis results. Authors claim there is no evidence of publication bias. It should be noted that some of the studies relating to PCT were not included in this meta-analysis, which would have an impact on their final results.

Conclusion:

The current literature on serum and pleural fluid PCT is conflicting. This may be due to the small number of participants and retrospective nature of the studies. Considering the papers in this review, the overall sensitivity and specificity of s-PCT for diagnosing pleural infection ranges from 69-83 % and 80-94 %, respectively. For pleural fluid PCT, sensitivity ranges from 45-80% while specificity is reported between 72-77%. It should be noted all studies used different cut-off values.

The evidence base does not justify the routine use of serum or pleural fluid PCT for the diagnosis of pleural infection. Similarly, with respect to monitoring response to treatment, serum PCT is not shown to be superior to CRP or LCC. Furthermore, there does not appear to be a prognostic role for s-PCT in predicting mortality or need for thoracic surgery. Large, prospective studies with stringent eligibility criteria and appropriate control populations, are required to further explore this topic.

Key points:

- **Insufficient evidence to support routine use of serum or pleural fluid procalcitonin for diagnosis of pleural infection**
- **Serum procalcitonin is no superior to CRP or leukocyte count when monitoring response to treatment in pleural infection**
- **Baseline serum procalcitonin was no superior to CRP or leukocyte count in predicting which patients would require surgery for management of pleural infection**

Conflicts of interest

The authors report no conflicts of interest.

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* This is a large study of 425 consecutive patients presenting to a tertiary pleural centre. There were 80 patients with pleural infection in this cohort and the diagnosis of pleural infection was independently verified by 2 consultants. The control group included other common causes of pleural infection. This study was unable to show a role for Procalcitonin in diagnosing pleural infection. They also demonstrated that baseline procalcitonin had no role in predicting which patients are more likely to require surgical management.

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* This is another large study with 308 patients, investigating the role of a number of pleural fluid markers for diagnosing pleural infection and differentiating between different sub-groups of PPE. 98 of the patients were with complex PPE and empyema. The study cohort also included uncomplicated PPE, tuberculosis and a control population of transudates and malignant pleural effusions. The authors concluded that procalcitonin had no role in diagnosing pleural infection.

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