

# The role of procalcitonin in adult patients with community-acquired pneumonia – a systematic review

Peter Berg & Bjarne Ørskov Lindhardt

## ABSTRACT

**INTRODUCTION:** Promising results in relation to severity assessment and treatment of patients with community-acquired pneumonia (CAP) have recently been presented from the study of procalcitonin (PCT) levels in these patients.

**METHOD:** A systematic search in PubMed and the Cochrane Library was conducted. Articles in English, German and Swedish were searched to investigate the role of PCT in adults with CAP.

**RESULTS:** The most thoroughly studied topic is the prediction of complications and death during hospital stay. PCT has predictive properties comparable to those of the Pneumonia Severity Index and the CURB65 scoring systems, and it may represent an addition to these indices. Furthermore, PCT levels may indicate aetiology as patients with typical bacterial infection have higher PCT levels than patients with atypical and viral aetiologies. The literature also indicates that PCT can distinguish CAP from asthma and acute exacerbation of chronic obstructive pulmonary disease. Several studies and a meta-analysis have shown that administration of antibiotics according to a PCT algorithm in a hospital setting reduced the use of antibiotics with no evidence of an increased risk.

**CONCLUSION:** PCT should only be an adjunct to the clinical examination and should be regarded a prognostic rather than diagnostic factor. PCT may help to safely reduce antibiotic use, but more research is required. Limitations of the present study include the heterogeneity of the literature with regard to setup and quality, differences in biochemical methods and diagnostic criteria of CAP and, finally, the risk of publication bias.

Procalcitonin (PCT) was discovered in 1975 [1] after isolation of the pro-hormone from chickens. Its clinical potential remained unknown until 1993, when Assicot et al [2] found that PCT levels were markedly raised in children with severe systemic bacterial infections compared with non-infected children and children with local or viral infections. Furthermore, PCT levels tended to drop rapidly following antibiotic (AB) treatment. Several studies have subsequently confirmed the relation between inflammation and PCT. Much research during the past decade has focused on the role of PCT in community-acquired pneumonia (CAP). Progress in this field has been rapid and is the focus of this review.

## METHOD

The PubMed database and the Cochrane Library were used. PubMed was searched using the search terms *procalcitonin*, *PCT* or *biomarkers* in combinations with *community-acquired pneumonia*, *CAP* and *meta-analysis*. Initially, no language restrictions were applied. All hits were subsequently exported to a PubMed collection in which process duplicates were automatically deleted. This left 821 articles which were assessed for relevance according to title and abstract. Articles with the claimed goal of investigating the role of PCT in adult patients with CAP were included. We excluded articles about children, articles that were not about patients with CAP, articles in which the field of interest was restricted to a few specific pathogens and articles that did not investigate the role of PCT. This left 73 articles for analysis of which seven were excluded due to language (three Polish, two Chinese, one Japanese and one Spanish); two were excluded for being only comments on other articles being assessed; one article was excluded because it was a summary of another article which was already included; one was excluded for being only a protocol; and, finally, 31 reviews (not meta-analyses) were excluded. One article was obtained from other sources.

The Cochrane Library was searched using the key words "Procalcitonin community acquired pneumonia", "Procalcitonin CAP" and "PCT CAP" This resulted in a total of four articles of which two were excluded for not addressing the topic in question, one for being in Chinese and the final article had already been included via PubMed.

Articles chosen for final inclusion comprised one meta-analysis, four randomized controlled trials (RCT), 24 prospective observational studies, one case-control study and one case study. An additional two articles were specifically searched for as references to the introduction of this work [1, 2].

## RESULTS

### Procalcitonin as a marker of prognosis and severity of community-acquired pneumonia

PCT as a marker of prognosis and severity of CAP is the topic of most articles (n = 17). A cohort study [3] with 96 elderly patients with CAP showed a correlation between initial PCT and CRP with a correlation coefficient of 0.31

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Department of Respiratory and Infections Medicine, Hillerød Hospital

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( $p = 0.002$ ). Furthermore, patients with bacteraemia had a PCT  $> 0.5$  ng/ml, and, finally, an acute physiology and chronic health evaluation (APACHE) II-score was correlated with PCT ( $p = 0.006$ ). The study cohort was small and only 55% had a PCT  $> 0.1$  ng/ml. This should be seen in light of the fact that studies from before approximately 2005 mostly used the LUMItest (Brahms) with a functional detection level of  $\sim 0.3$  ng/ml [4]. Another study [5] included 110 intensive care unit patients with CAP. Nine out of ten with bacteraemia had PCT  $> 2$  ng/ml and the last patient had a PCT of 1.8 ng/ml. A strong correlation was found with septic shock (5.1 ng/ml (95% confidence interval (CI): 2.4-41) versus 1.4 (0.6-5.4) ( $p = 0.0002$ ), number of organ failures ( $p = 0.0001$ ) and occurrence of complications ( $p = 0.001$ ). Patients who died had higher mean PCT levels than survivors. Limitations of the study were, among others, the use of a broader definition of CAP than seen in other studies, including "altered mental status". Similar findings for both initial PCT and PCT kinetics have later been reported [6-8]; however, Heppner et al [7] only enrolled 17 patients and did not define CAP sufficiently. Menéndez et al [9] investigated the predictive value of PCT for treatment failure within 72 hours. PCT proved predictive on day 1 ( $p = 0.0001$ ) with a median PCT of 0.5 (95% CI 0.3-2.2) versus 1.5 (0.4-7.1). On day 3 PCT was still predictive ( $p = 0.004$ ). Sensitivity for PCT was 57% and specificity 75%, positive predictive value 17% and negative predictive value 95%. In another study by Menéndez et al [10], PCT at admission was found to correlate with the pneumonia severity index (PSI) ( $p = 0.001$ ) and CURB-65 scores (confusion, urea  $> 7$  mmol/l, respiratory rate

$> 30$ /min, systolic blood pressure  $< 90$  mmHg and age  $> 65$ ) ( $p = 0.0001$ ) as similarly reported by others [8, 11-14]. Those who died within 30 days had a significantly higher initial PCT level than survivors (median 1.8 (interquartile range (IQR) 0.63-13.07) versus 0.58 (0.27-2.38) ( $p = 0.002$ ), but the area under the receiver operating characteristics curve (AUC) for PCT was only 0.66 (0.56-0.76).

In 2008, the German study group CAPNETZ published results from a study with 1,404 adult patients [15]. The end point was death within 28 days. The death rate percentages in four groups based on CRB-65 score (confusion, respiratory rate  $> 30$ /min, systolic blood pressure  $< 90$  mmHg and age  $> 65$  years) were 4, 12, 18 and 67%, respectively, and PCT levels were accordingly higher ( $p < 0.0001$ ). The AUC for PCT as predictor of death was 0.80 (0.75-0.84) and did not differ significantly from that of CRB65. The optimal prognostic accuracy was obtained with a cut off of 0.228 ng/ml (sensitivity 84.3 (73.6-91.9), specificity 66.6 (64.1-69.0), positive predictive value 10.7%, negative predictive value 98.9%). The most important limitation is the fact that CRB-65 groups four and five only included 44 and six patients, respectively, out of the 1,404 subjects. Comparable findings were made by Huang et al [13] who used an algorithm to anticipate death within 30 and 90 days, length of hospital stay and risk of admission to an intensive care unit (ICU). A total of 1,651 adults with diagnosed CAP were equally distributed between PCT groups:  $< 0.1$  ng/ml = 32.8%, 0.1-0.25 = 21.6%, 0.26-0.5 = 10.2%,  $> 0.5$  = 35.4%. The PSI, CURB-65 (CRB65 with the addition of urea  $> 7$  mM as a parameter) and the lowest PCT group were all predictive of a lower 30-day mortality. In the high risk groups, 23.1% had a PCT  $< 0.1$  and, interestingly, the 30-day mortality in this group as was similar (1.6%) to that of the low risk groups (PSI I-III and CURB65 0-1). A problem with this study could be the presence of selection bias as the cohort was chosen from a randomised controlled trial, where about a quarter of the patients meeting the inclusion criteria refused to participate. The CAPNETZ group published a work on the association between all-course mortality within 28 and 180 days and several biomarkers [16]. PCT was higher in those who died ( $< 28$  d.:  $p = 0.0135$  and AUC 0.65,  $< 180$  d.:  $p = 0.0273$  and AUC 0.58). In conclusion, there was an association with PCT, but it was not useful, and the cardiovascular precursors pro-atrial natriuretic peptide (pro-ANP) and pro-adrenomedullin proved superior to PCT, as also reported by Claessens et al [17]. Noteworthy are the large differences in baseline data between survivors and non-survivors.

Schuetz et al [18] published results from a RCT (the proHOSP study) with 925 CAP patients. The goal was to assess death rate, rate of complications, side effects of



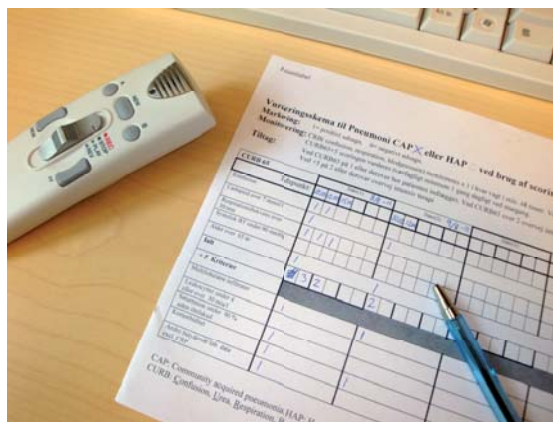
## ABBREVIATIONS

AB = antibiotic  
 ADL = activities of daily living  
 AECOPD = acute exacerbation of chronic obstructive pulmonary disease  
 APACHE = acute physiology and chronic health evaluation  
 AUC = area under the curve  
 CAP = community-acquired pneumonia  
 CI = confidence interval  
 CC = correlation coefficient  
 COPD = chronic obstructive pulmonary disease  
 CRB-65 = confusion, respiratory rate  $> 30$  /min, systolic blood pressure  $< 90$  mmHg and age  $> 65$  years  
 CRP = C-reactive protein  
 CURB65 = confusion, urea  $> 7$  mmol/l, respiratory rate  $> 30$  /min, systolic blood pressure  $< 90$  mmHg and age  $> 65$  years  
 ICU = intensive care unit  
 IQR = interquartile range  
 LRTI = lower respiratory tract infection  
 PCT = procalcitonin  
 Pro-ANP = pro-atrial natriuretic peptide  
 PSI = pneumonia severity index  
 RCT = randomized controlled trial  
 ROC = receiver-operating characteristics  
 VAS = visual analogue scale  
 WBC = white blood cell count

AB and the duration of treatment in a group treated according to the above-mentioned PCT algorithm and a group in which a standard approach was used. The rate of adverse outcomes was insignificantly lowered, as was the death rate; however, the algorithm was overruled in 20% of the patients. A follow-up study [14, 18] showed that initial PCT could not predict 30-day mortality (AUC 0.60 (0.52-0.67), and peak PCT was only slightly better in that respect. PCT, PSI and CURB65 were similar with regard to prediction of complications and ICU admission. For disease-specific complications, both initial and peak PCT proved better than the scoring systems. In patients with low PSI and CURB-65, PCT showed a correlation with complications ( $p < 0.001$ ). The same correlation was seen in high-risk patients based on CURB-65 ( $p = 0.006$ ), but not with PSI ( $p = 0.07$ ). In those with any complication including death, the median PCT was significantly higher on days 5 and 7 ( $p < 0.01$ ). A cohort study [19] with 394 patients that compared PCT with clinical stability based on vital parameters and outcome after 72 hours concluded that patients who were unstable at 72 hours had significantly higher median PCT levels than those who were stable at both day 1 ( $p = 0.0003$ ) and day 3 ( $p = 0.003$ ). In a logistic regression analysis, PCT proved not to be an individual predictor of severe complications and PCT did not improve the AUC when added to a receiver-operating characteristics curve (ROC) analysis, where clinical stability at 72 hours was used as a predictor of severe complications (0.77 (0.63-0.91)  $p = 0.45$ ). However, patients with PCT  $< 0.25$  ng/ml and clinical stability at 72 hours did not experience severe complications.

#### Correlation between procalcitonin and aetiology

The second-most studied area is the correlation between PCT and aetiology. Hedlund & Hansson [3] found that PCT was significantly lower in patients with atypical (*Mycoplasma*, *Chlamydomphila*, *Legionella*) than typical bacterial aetiology of CAP ( $p = 0.03$ ) – a correlation also reported by Krüger et al [20] with an AUC of 0.69 (0.66-0.71) at a cut-off value of 0.1 ng/ml and an odds ratio (OR) of 8.3 (95% CI 4.8-14.5). With a cut-off value of 0.25, the OR was 3.2 (2.1-5.0). No differences in biomarkers were seen between patients with different types of atypical aetiologies or between atypical and viral CAP. A study by Piacentini et al [21] likewise found higher PCT levels in patients with bacterial CAP than with H1N1 CAP: The study, though, was very small. Boussekey et al [5] reported that in their study, 80% ( $n = 88$ ) of patients with *Streptococcus pneumoniae* had a PCT  $> 2$  ng/ml compared with 40% of those who did not obtain an aetiological diagnosis. A study of 240 CAP patients with bacterial and viral CAP in 2005 [22] found that differences in PCT were non-significant ( $p = 0.08$ ),



The CURB65 scoring system for severity assessment of pneumonia patients is widely used across the world – the image shows an extended version used by Hillerød Hospital.

although they tended to be higher in bacterial CAP. A study from South Africa [23] found significant differences in PCT between patients with lung tuberculosis, *Pneumocystis jirovecii* and “classic” bacterial CAP. A correlation between PSI and PCT was found ( $p = 0.01$ , correlation coefficient (CC) 0.256). Furthermore, no difference in PCT levels was found between HIV-positive and HIV-negative patients. HIV has been used as an exclusion criterion in several studies due to immunosuppression. A limitation of this study [23] is that no age was reported; 83% were HIV-positive, the death rate was very high (14%) and no definition of CAP symptoms was reported.

In a small study ( $n = 30$ ) [24], the median PCT was significantly higher in patients with typical than in patients with atypical CAP: 7.64 ng/ml (range 0.26-63.16) versus 0.80 (0.13-34.90)  $p = 0.031$ . However, the AUC was 0.745 with a wide 95% CI (0.555-0.935). More results from the study by Schuetz et al from 2009 [18] were published in 2010 [25]. Here, the median PCT was higher in patients with a positive blood culture ( $p < 0.0001$ ) and all patients with positive blood cultures had a PCT  $> 0.25$  ng/ml within three days. The conclusion was that a PCT cut-off of 0.25 ng/ml would result in 37% less cultures while still detecting 96% of the positive cultures; however, a negative culture does not rule out bacterial infection.

#### The diagnostic properties of procalcitonin

A case-control study [26] using the LUMItest which included 26 patients with CAP found no value of PCT at a cut-off of 0.5 ng/ml, but a receiver-operating characteristics (ROC) analysis led to an optimal cut-off of 0.245 – very close to the best proposals for detecting bacterial infection [8, 18, 27, 28]. Another study [11] with a cohort of 373 subjects demonstrated that PCT with an AUC of 0.85 (0.80-0.91) was significantly better than C-reactive protein (CRP), white blood cell count (WBC) and temperature  $> 38^{\circ}\text{C}$  to diagnose CAP and that PCT improved the ability of clinical findings to diagnose CAP ( $p < 0.001$ ). This study postulated that a PCT  $< 0.1$  ng/ml

indicates another diagnosis than CAP – even with infiltrate on X-ray. Bafadhel et al [29] conducted a cohort trial with 319 patients of whom 96 had CAP. Patients with pneumonia had a higher PCT ( $p < 0.0001$ ) than those with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). At a cut-off of 0.08 ng/ml, PCT had an AUC of 0.93 (0.88-0.98) for differentiation between pneumonia and asthma; sensitivity 89% (95% CI 78-95) and specificity 78% (95% CI 72-82). Interestingly, as opposed to other findings [30], there was no effect on PCT when patients were pre-treated with AB.

#### Using procalcitonin to reduce antibiotic exposure

Christ-Crain et al [27] published a study using the PCT-based algorithm mentioned above. The relative risk of AB exposure adjusted for confounders in the PCT-guided group was 0.49 (95% CI 0.44-0.55,  $p < 0.0001$ ) and patient safety was not compromised. These findings were promising, but the follow-up period was only 14 days. The study was repeated in larger scale [31] with the same findings, which were also strongly supported by Schuetz et al [18, 32], Müller et al [11] and a meta-analysis [28].

#### The usefulness of procalcitonin in primary care

Only two studies have evaluated the usefulness of PCT in primary care. The first from 2007 [33] excluded patients requiring hospitalization. A total of 357 patients with suspected lower respiratory tract infection (LRTI) were included with the aim of studying if PCT can predict an infiltrate on chest X-ray and bacterial infection. 10% had PCT  $< 0.02$  ng/ml and 61%  $< 0.06$ . The median value was 0.05 (IQR 0.04-0.08, total range 0.02-42.92). The AUC for prediction of an infiltrate with PCT ( $> 0.06$  ng/ml) was 0.73 (CI not shown). The AUC for prediction of bacterial infection was 0.61. The low PCT levels obviously made PCT less useful, but these findings are in line with the above-mentioned correlation between PCT and

PSI as the hospitalized patients were excluded. However, the findings contradict those reported in a study conducted by Briel et al [34]. In the study by Briel et al, 458 adults were studied to assess the number of days with limitations in activities of daily living (ADL), AB use, discomfort on a visual analogue scale (VAS) and days off work after implementation of the above-mentioned PCT algorithm in the intervention group. No differences were seen in days of ADL restriction with or without the use of the algorithm. AB usage was reduced by 48% in CAP patients and by 80% in patients with upper respiratory tract infection (RTI). Only approximately 10% in the intervention group were treated in violation of the algorithm. Number of days off work did not differ significantly between groups and subjective discomfort measured on a 10-point VAS scale was only 0.8 (95% CI 0.4-1.2) points higher in the intervention group than in the control group and thus considered equal in the two groups. Limitations include the broad inclusion criteria applied which limits comparability with other studies. Also, p values for the differences in baseline characteristics are not shown.

#### Procalcitonin and corticosteroids

Many studies exclude immunosuppressed patients including those receiving corticosteroid treatment. The influence of corticosteroids on PCT and CRP was assessed in a case-control setting [35]. No differences were found; however, only ten patients were included in each group and cases who were all treated with a fixed dose of corticosteroids had underlying chronic obstructive pulmonary disease (COPD), while controls did not have COPD, and the comparability can thus be discussed.

#### DISCUSSION

In patients with CAP, PCT has been most extensively studied with regard to its prognostic value and correlation with disease severity. This review shows that complications during admission, severity of disease measured with various scales (mostly PSI, CRB-65 and CURB-65) and, to a lesser extent, death within a month all tend to correlate with higher PCT levels – especially  $> 0.50$  ng/ml. However, no definite cut-off has been found, and PCT should always be interpreted carefully and compared with the results of the clinical examination. PCT should furthermore be regarded a prognostic rather than diagnostic factor.

The evidence of PCT as a predictor of aetiology is less well-studied, but results in this field are promising. Many authors report significantly higher levels of PCT in patients with typical bacterial aetiologies than in patients with atypical and viral ones. The most frequent conclusion is that a PCT  $> 0.25$  ng/ml more often reflects a typical bacterial aetiology and calls for an extra effort



#### TEXT BOX

Procalcitonin (PCT) is a biomarker of inflammation.

Several studies have found that PCT level measured at hospitalization in patients with community-acquired pneumonia correlate with disease severity measured by scoring systems like the Pneumonia Severity Index and CURB-65.

The amount of circulating PCT tends to be lower in patients with legionella, chlamydia, mycoplasma (“atypical” aetiologies) or a viral aetiology than in patients with typical bacterial findings like *Streptococcus pneumoniae*.

This biomarker may have the potential to guide physicians in their decision to prescribe antibiotics without compromising patient safety, but more research is needed.

PCT is a prognostic rather than diagnostic factor and must always be interpreted in relation to clinical examination, anamnesis and laboratory/radiographic findings.



in detecting the infectious agent. No differences have been found between atypical and viral causes of CAP.

These findings have contributed to the development of PCT-guided algorithms for administration of antibiotics in patients with LRTI. Large and methodologically thorough studies and a meta-analysis have consistently and convincingly shown that a substantial reduction in AB usage is achievable without compromising patient safety.

Many aspects of PCT seem to mimic those of CRP: Both are so-called “positive” acute phase reactants, both markers increase and decrease rapidly as infection and inflammation come and go, both seem to be induced by the host response to these changes, and a correlation between levels of PCT and CRP reported by Hedlund & Hansson in 2000 have been confirmed several times [9, 10, 19, 29]. Indeed, PCT is sometimes described as a “CRP-like” substance. This is roughly true, but there are important differences and they are clinically relevant. One issue is the correlation between PCT and PSI/CRB65/CURB65 [10, 14, 15, 20] – which has not been matched by CRP. In addition, the aforementioned difference in PCT levels in viral and bacterial CAP is another subject specific to PCT, and a plausible connection between PCT and bacteremia has not been found for CRP [11, 25]. All in all, PCT has shown a greater predictive value than CRP in the clinical risk assessment of CAP patients and appears to be more specific for bacterial aetiologies. CRP, on the other hand, is more widely available, has a larger base of experience in a wider range of conditions and is currently cheaper than PCT. Hence CRP is, in contrast to PCT, measured by default in all newly hospitalized patients, and for now, PCT should be considered a biomarker with a narrower and somewhat different indication than CRP as shown above; yet, it offers great potential.

Some general issues of concern can be made regarding the available literature. Firstly, more large studies with patient numbers > 1,000 are needed since the interpretation of a given PCT value is difficult, and valid cut-offs are needed. Secondly, an objective and widespread gold standard for the diagnosis of CAP is missing. This compromises comparability of the literature. Also, studies of aetiology are biased as a negative blood culture does not rule out bacterial infection. In addition, the studies used a panel of three different methods to measure PCT (LUMItest, Kryptor, and Liaison PCT) with three different functional detection levels. This affects comparability and makes it difficult to determine cut-off levels of PCT. Finally, one must consider the possibility of publication bias, which could lead to an overestimation of the usefulness of PCT. Future research should focus on the algorithm, especially in primary care where antibiotic expenditure is often based on clinical

findings and the research results presented [33, 34] are contradictory. Also, it is imperative that the most sensitive biochemical methods are used for assessment if relevant cut-offs are to be defined.

**CORRESPONDENCE:** Peter Berg, Lunge- og Infektionsmedicinsk Afdeling, Hillerød Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark.

E-mail: soccus@gmail.com

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**CONFLICTS OF INTEREST:** none

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