Serial procalcitonin measurements for managing community-acquired pneumonia

January 2017

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Summary

Procalcitonin (PCT) is a biomarker which is elevated in bacterial infection. Usefulness of PCT measurements in community-acquired pneumonia (CAP) has to be proven by many studies.

A single measurement of PCT on admission or outpatient visits is useful to diagnose CAP, estimate causative pathogens pattern, and for assessment of the severity of pneumonia and prognosis in CAP.

Serial measurements of PCT in CAP patients are useful for predicting prognosis, evaluating initial treatment effect and stopping antibiotic therapy.

We may improve medical care in CAP by measuring PCT consecutively.

Introduction

Community-acquired pneumonia (CAP) is a disease with high morbidity and mortality. The mortality of CAP was reported to be 7.3%, 9.1% and 13.3% in the United States of America/Canada, Europe and Latin America, respectively [1]. In management of CAP, diagnosis of pneumonia, identification of causative microorganisms and appropriate therapy are very significant.

Biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” by the National Institutes of Health [2].

An ideal biomarker in management of CAP should have high sensitivity and specificity in diagnosis of CAP, in estimation of causative pathogens, and in assessment of severity and prognosis, and it should be useable as an indicator of when to stop giving antibiotics.

Unfortunately, there are no biomarkers to satisfy all these requirements at the same time currently. Therefore we use a combination of various clinical and laboratory biomarkers to diagnose CAP, estimate causative pathogens, assess severity and prognosis, and stop antibiotic therapy.

Procalcitonin (PCT) is the precursor of calcitonin which is a 116-amino acid peptide and produced by the C-cells in the thyroid. PCT in the serum of healthy individuals is very low (<0.1 ng/mL). However, if bacterial infection occurs, PCT is released in a cytokine-like manner by a variety of parenchymal cells, including liver, kidney, and lung, but not by leukocytes [3].

Its concentration can be more than a 1,000-fold increase in blood. Assicot *et al*. [4] reported that PCT increased in patients with bacterial infection. After that, many studies about the usefulness of PCT in the management of CAP have been reported. In this review, I will focus on the role of serial PCT measurements in the management of CAP, especially in diagnosis, estimation of causative pathogens and assessment of pneumonia severity and prognosis.

Diagnosis of community-acquired pneumonia

We use symptoms such as cough, sputum, fever, dyspnea and chest pain as clinical biomarker in diagnosing pneumonia. Indeed, Infectious Disease Society of America and American Thoracic Society defined that patients with clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) plus infiltration of lung by chest radiography are diagnosed CAP [5].

However, clinical symptoms and physical examination findings may be lacking in elderly patients [6]; in such a case, the diagnosis of CAP would be difficult.

The usefulness of PCT for predicting CAP in a primary care setting was reported [7]. In this study, which included 364 adult outpatients with lower-respiratory-tract infection we used PCT cut-off >0.06 ng/mL and saw that the sensitivity of predicting radiographic pneumonia and subsequent hospitalization were 0.70 and 0.67.

However, positive predictive values were too low to be of use in clinical practice. Eleven CAP patients (23%) had PCT values >0.25 ng/mL whereas only four non-CAP patients (1%) had PCT values >0.25 ng/mL. Therefore we may use PCT >0.25 ng/mL to rule in bacterial CAP.

Müller *et al* [8] evaluated the diagnostic accuracy of symptoms and laboratory findings and different parameters, including PCT, highly-sensitive C-reactive protein (hsCRP) and leukocyte count (WBC) for diagnosing CAP in 545 patients with suspected lower-respiratory-tract infection. PCT had a significantly (p<0.001) higher diagnostic accuracy in differentiating CAP from other diagnoses compared to hsCRP, WBC and body temperature, see Table I.

	AUC (95% CI)
PCT	0.88 (0.84-0.93)
hsCRP	0.76 (0.69-0.83)
WBC	0.69 (0.62-0.77)
Body temperature	0.55 (0.46-0.63)

Table I

When only symptoms including fever, cough, sputum production, abnormal chest auscultation and dyspnea were used, AUC was 0.79. This value was significantly (p<0.001) increased by adding PCT, see Table II.

	AUC (95 % CI)
Symptoms	0.79 (0.75-0.83)
Symptoms + PCT	0.88 (0.85-0.91)

Table II

Organizing pneumonia (OP) is one of the differential diagnoses of infiltration on chest radiography with respiratory symptoms.

In the study measuring PCT in histopathologically proven OP (N=15) and hospitalized CAP (N=15), PCT levels in the OP group (0.14 ng/mL, IQR: 0.09-0.27 ng/mL) were significantly lower compared to CAP (2.6 ng/mL, IQR: 0.39-5.7 ng/mL). Thus PCT may be a useful biomarker for differentiating CAP from OP. However, the number of patients was small in the study.

Concerning the diagnosis of CAP, the lower level of PCT (e.g. <0.25 ng/mL) cannot exclude bacterial pneumonia because we see the bacterial CAP patient whose PCT level is less than 0.25 ng/mL, especially in patients with mild to moderate severity. However, higher PCT levels may be useful to predict bacterial pneumonia although we must pay attention to the fact that PCT levels are also sometimes high in fungal infection.

Estimation of causative microorganisms

Some studies have reported the usefulness of PCT in estimating etiologic pattern of CAP. Hedlund *et al* [9] showed that median PCT levels in classic bacterial (N=27) and atypical agents (N=9) were 1.41 ng/mL (range: 0.05-64.99 ng/mL) and 0.05 ng/mL (range: 0.05-7.49 ng/mL), respectively.

On the other hand, median CRP levels were 192 mg/L (range: 47-367 mg/L) and 188 mg/L (range: 102-325 mg/L), respectively. Patients with low PCT levels on admission were more likely to have a pneumonia caused by atypical agents (p<0.03); however, CRP levels on admission in these two groups did not differ significantly (p=0.71).

Krüger *et al* [10] indicated that patients with proven typical bacterial etiology showed significantly higher PCT levels, CRP levels and WBC compared to patients with atypical or viral etiology (p<0.01). When PCT cut-off level of 0.1 ng/mL was used, an odds ratio to differentiate Streptococcus pneumoniae CAP from CAP due to atypical or viral pneumonia was 8.3 (95% CI: 4.8-14.5), and when PCT cut-off level of 0.25 ng/mL was used, the odds ratio was 3.2 (95% CI: 2.1-5.0).

Levels of PCT were comparable in patients with atypical or viral pneumonia. They also reported that levels of PCT in Legionella pneumophila (N=48), Mycoplasma pneumoniae (N=140) and Chlamydia pneumoniae (N=2) were 0.20 ng/mL (IQR; 0.02-41.77 ng/mL), 0.10 ng/mL (IQR; 0.01-12.14 ng/mL) and 0.03 ng/mL (IQR; 0.02-0.04 ng/mL), respectively. In these patients with CAP due to three microorganisms, there were no significant differences in PCT.

Regarding estimation of causative pathogens in CAP, we could estimate the CAP etiology, whether bacterial or atypical and viral, by using PCT. However, there are few reports about PCT levels compared to each microorganism at present, and I think it would be impossible to differentiate causative pathogens by PCT levels.

Severity assessment and predicting prognosis in pneumonia

There are some reports that PCT levels on admission correlate with the severity of pneumonia and prognosis [8, 11, 12]. Furthermore, some reports have shown that consecutive PCT measurements are useful for predicting prognosis in CAP [13, 14, 15].

A prospective cohort study including 240 CAP patients in Spain showed that patients with Pneumonia Severity Index (PSI) class III-V had a significantly higher mean PCT value of 0.67 µg/L (range: 0.10 to 10.57 µg/L) than those of PSI class I-III (mean: 0.31 µg/L; range: 0.10 to 8.95 µg/L;

p=0.01) [11]. It also showed that patients with complications (including empyema, mechanical ventilation requirement, or septic shock) or who died had a higher PCT level than those who did not (p=0.03 and p<0.0001, respectively).

The CAPNETZ study [12] conducted in 10 local clinical centers throughout Germany, including 1671 CAP patients, reported that when the severity was assessed by the so-called CRB-65 score, the PCT levels correlated with the severity of CAP, but CRP and WBC did not. Median PCT levels on admission of non-survivors were significantly higher compared with those in survivors (0.88 vs 0.13, p<0.0001).

The accuracy of PCT, CRP, WBC and CRB-65 to predict death at 28 days was analyzed, the AUC was highest for PCT (0.80), which was not significantly different compared with CRB-65 score (0.79), which, however, was significantly higher than CRP (0.62, p<0.01) and WBC (0.61, p<0.01). The combination of PCT and CRB-65 use improved the accuracy to predict death (AUC 0.83, p<0.01 compared with CRB-65 alone).

We showed the usefulness of serial PCT measurements to predict prognosis and initial treatment failure in CAP patients [15]. We measured PCT serially on admission (Day1) and 48 to 72 hours after admission (Day3). We used the ratio of PCT

	30-day mortality rate % (dead patients/all patients)	
	Admission (Day 1)	Day 3
New scoring system, points		
0	0 (0/95)	0 (0/44)
2	4.4 (8/182)	2.4 (4/166)
3	21.8 (12/55)	12.3 (9/73)
4	ND	50.0 (8/16)
Non-weighted scoring system, points		
0	0 (0/95)	0 (0/44)
1	4.2 (9/215)	1.4 (3/214)
2	21.8 (12/55)	11.0 (10/91)
3	ND	50.0 (8/16)

TABLE III: Thirty-day mortality rate according to the new scoring system and the non-weighted scoring system [15]

New scoring system:
- CRP Day1 ≥ 100 mg/L ~ 2 points
- CURB-65 ≥ 3 ~ 1 point
- PCT Day3/Day1 ≥ 1 ~ 1 point

Non-weighted scoring system:
- CRP Day1 ≥ 100 mg/L ~ 1 point
- CURB-65 ≥ 3 ~ 1 point
- PCT Day3/Day1 ≥ 1 ~ 1 point

ND = no data

	PCT Day3/Day1≥1 N = 119 N (%)	PCT Day3/Day1<1 N = 246 N (%)	p value
30-day mortality	14 (11.8)	7 (2.8)	0.001
Initial treatment failure	26 (21.8)	26 (10.6)	0.006

Day3/Day1 ≥ 1 to see whether this is useful for predicting prognosis and initial treatment failure. We introduced a new scoring system.

To predict prognosis of CAP, we used not only CURB-65 ≥ 3, CRP ≥ 100 mg/L on admission and but also used PCT levels Day3/Day1 ≥ 1 on Day3. Using this scoring system, if both criteria – CURB-65 ≥ 3 and CRP ≥ 100 mg/L – were met on admission, the 30-day mortality rate was 21.8%, and in case PCT Day3/Day1 ≥ 1 was met on Day3, the 30-day mortality increased to 50%, see Table III.

The effect of initial therapy was evaluated. The rate of initial treatment failure in patients with PCT Day3/Day1 ≥ 1 was significantly higher than in patients with PCT Day3/Day1 < 1 (21.8% vs 10.6%, p=0.006), see Table IV.

If a CAP patient meets PCT Day3/Day1 ≥ 1 on Day3, 30-day mortality rate and initial treatment failure rate are high, and we may need to change antimicrobials or closely monitor instead of changing antimicrobials.

It would be useful to measure PCT on admission for assessing severity of pneumonia and prognosis, and serial measurements of PCT are more useful for predicting prognosis and initial treatment failure.

Conclusions

PCT is a useful biomarker in managing of CAP, including diagnosis, estimation of causative pathogens, assessment of severity and prognosis, and treatment monitoring.

By measuring PCT serially, we may improve medical care in CAP.

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