

Serum Procalcitonin in Lower Respiratory Tract Infections in Adult Patients

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Abstract

Procalcitonin is a protein (that consists of 116 amino acids) and is a peptide precursor of the hormone calcitonin. Calcitonin is involved in the homeostasis of calcium. In healthy people, procalcitonin blood levels are negligible. Based on the current data, raised serum procalcitonin levels indicate activation of the innate immune system due to invasion of microbes (bacteria, some fungi, and malaria). Procalcitonin levels are used to support the diagnosis of bacterial infection or sepsis in the emergency departments. This biomarker can be used, along with clinical judgment, in a hospital setting to guide antibiotic treatment in cases of pneumonia and non-pneumonic lower respiratory tract infections.

Keywords: procalcitonin, calcitonin, pneumonia, lower respiratory tract infections, guiding antibiotics therapy

Abbreviations: TNF = tumour necrosis factor, IL = interleukin, CAP = community acquired pneumonia, VAP = ventilator associated pneumonia, COPD = chronic obstructive pulmonary disease, AECOPD = acute exacerbation of COPD

Background

In the absence of systemic inflammation, procalcitonin synthesis is mainly restricted to the neuroendocrine cells of the thyroid.¹ This is not released into the blood until cleaved/mature form (i.e. calcitonin). Therefore, procalcitonin levels remain undetectable.² Almost all body tissues can produce procalcitonin. The main triggers for its synthesis are bacterial toxins (endotoxins) and cytokines released in response to bacterial infections (TNF alpha, IL-1-beta and IL-6). See Table 1. Cytokines released due to viral infections (e.g. interferon-gamma) inhibit TNF-alpha production.^{1, 3} During an inflammatory response, procalcitonin levels start rising within 2-4 hours and peak in 24-48 hours. Peak levels correlate to the severity of the bacterial infection. When inflammation resolves, procalcitonin levels fall quickly, falling by 50% every 24-36 hours. If the inflammation is ongoing, procalcitonin levels plateau (due to ongoing production of procalcitonin).⁴

Table 1: Points to remember: ⁵⁻¹¹

1. Most bacterial infections will cause a rise in procalcitonin levels (levels >0.25ng/ml).
2. The following bacterial infections will not cause a rise in procalcitonin levels:
 - a. Mycoplasma pneumoniae.
 - b. Chlamydia pneumoniae.
3. Parapneumonic effusions, empyema and lung abscesses may not cause a rise in procalcitonin levels.
4. Mycobacterium tuberculosis, can and can't cause a rise in the procalcitonin levels
5. Viral infections will not cause a rise in procalcitonin levels (levels <0.25ng/ml).
6. Amongst fungal organisms, candida infections can cause a rise in

procalcitonin levels (levels >0.25ng/ml).

7. Malaria can cause a rise in procalcitonin levels (levels >0.25ng/ml).

8. Clostridium difficile colonization will not cause a rise in procalcitonin levels (levels <0.25ng/ml).

9. Lung cancers (especially neuroendocrine) and medullary thyroid cancers can cause a rise in procalcitonin levels (levels >0.25ng/ml).

10. Renal insufficiency (which hinders the clearance) can cause a rise in the baseline procalcitonin levels.

11. Physiological stress can cause a rise in procalcitonin levels (levels >0.25ng/ml). This includes trauma, surgery, burns, bowel ischemia, cerebrovascular accident (infarct and haemorrhage), pancreatitis and any kind of shock-like situation.

Community Acquired Pneumonia (CAP) and Procalcitonin

As we know, it can take 24-48 hours for the procalcitonin to reach its peak levels, hence in an acute clinical setting (where CAP is the diagnosis, or suspected), the decision to start antibiotics can't depend on the initial procalcitonin levels (because of high morbidities associated with CAP).

Nevertheless, serial levels will help in guiding antibiotic therapy.

- a. If procalcitonin levels are persistently <0.25ng/ml in a CAP patient with suspected viral aetiology (based on history and investigations), antibiotics can be stopped. We should keep in mind that procalcitonin levels do not normally rise in the case of mycoplasma and chlamydia pneumonia.
- b. Suspected or known CAP patients should receive empiric antibiotics as per local protocol in an acute setting.
- c. Antibiotics can be stopped in patients with suspected or known bacterial CAP who have received antibiotics for at least five days and shown clinical improvement with procalcitonin levels dropping <0.25ng/ml.

- d. CAP patients who are not clinically improving, and procalcitonin levels are rising or not decreasing, will need a review of antibiotics.
- e. Optimal threshold for discontinuing antibiotic therapy has not been established.¹²
- f. Procalcitonin levels have prognostic value. Again, there is no optimal threshold. Serial levels have more prognostic value than a single level.

Ventilator Associated Pneumonia (VAP) and Procalcitonin

Patients with VAP are usually very unwell. Antibiotics should be started as soon as VAP is suspected. Procalcitonin can be used to stop antibiotics in VAP patients. As per ProVAP trial, stopping antibiotics when procalcitonin level drops <0.5 ng/ml, or $\geq 80\%$ from its peak value, did not result in an adverse outcome.

Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and Procalcitonin

Use of procalcitonin to guide antibiotic therapy in patients with AECOPD has not been established yet. Some experts use the levels to help in making decisions about stopping antibiotics (in a similar way as mentioned in the above section of CAP). Infections in AECOPD are less invasive and pathogens differ from CAP; procalcitonin levels may not correlate well with the severity of the episode. In one trial, antibiotic use was found to be of no benefit in patients with AECOPD with levels <0.1 ng/ml.¹³

Acute Bronchitis and Procalcitonin

Mostly acute bronchitis is caused by viral infections and do not need antibiotics. In patients where the need for antibiotics is unclear, serum procalcitonin levels can help in making this decision.

Summary

Level (ng/ml)	Likelihood of bacterial infection
<0.10	Very unlikely
$0.10 - 0.25$	Unlikely
$0.25 - 0.50$	Likely
>0.50	Very likely

(This should aid clinical decision making i.e. decision should not be solely based on these levels).

In an acute clinical setting, where pneumonia is suspected or is the cause for sepsis, empirical antibiotics should be started according to a local protocol without considering the serum procalcitonin levels. If serial serum procalcitonin levels remain below 0.10 ng/ml on day 3, antibiotics can be stopped, aided by clinical judgment. The above-mentioned points should be kept in mind with the fact that certain bacterial infections do not cause a rise in serum procalcitonin levels. The levels also have prognostic value in case of CAP and VAP. Usually, acute bronchitis is a viral illness; if symptoms are not improving or bacterial infection is suspected, raised serum procalcitonin levels can aid the clinical judgment in starting antibiotics. In the case

of infective AECOPD, the levels are not very helpful in making a decision about starting antibiotic therapy. In respiratory tract infections, where the patient has received adequate duration of antibiotic therapy, and procalcitonin levels fall <0.10 ng/ml, treatment can be stopped safely (if clinical judgment allows). See Table 2.

Competing Interests

None declared

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