Editorial

Procalcitonin as a marker of bacterial infection in elderly patients

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Procalcitonin (PCT) is a peptide precursor of calcitonin that is released by parenchymal cells in response to bacterial toxins, leading to elevated serum levels in patients with bacterial infections; in contrast, procalcitonin is down-regulated in patients with viral infections. The dual function of PCT as a precursor peptide from the hormone calcitonin and a cytokine mediator, which is elevated upon systemic bacterial infections in line with other cytokines, has led to the term "hormokine" mediator[1].

PCT shows an earlier increase upon infection and a more rapid decrease when the infection is controlled by the immune system supported by antibiotic therapy. PCT correlates with the extent and severity of infection and has prognostic implications, as the course of PCT predicts the risk for mortality in critically ill patients with infections[2] and in patients with ventilator-associated pneumonia (VAP)[2-4]. Furthermore, the production of PCT, in contrast to other biomarkers including C-reactive protein (CRP), seems not to be significantly attenuated by non-steroidal and steroidal anti-inflammatory drugs[3-5].

The efficacy and safety of PCT-guided decision-making regarding antibiotics has been demonstrated in 14 randomized controlled trials in different clinical settings and including infections of varying severity[6,7]. A diagnostic algorithm has been proposed by Schuetz et al,[6] regarding the guidance of antibiotic therapy in different clinical settings and with different cut-off points of procalcitonin. In this algorithm, the patients are categorized in 3 groups of risk: A: Low risk, non pneumonic respiratory infections, B: Moderate risk, pneumonic infections in the emergency department and inpatients, C: High risk, sepsis in need of intensive care unit admission. For **group A patients**, initiation or continuation of antibiotics is strongly discouraged or discouraged respectively, for cut-off points <0.1μg/l and <0.25μg/l respectively. For cut off-points ≥0.25μg/l and >0.5μg/l, antibiotics are encouraged and strongly encouraged respectively. For **group B patients**, the recommendations of the algorithm are the same as for group A patients. For **group C patients**, empirical antibiotics are recommended for all patients irrespectively of the PCT value (Table 1).

Levels of serum procalcitonin, using the same algorithm, were also used to determine follow-up decisions. In group A patients, follow-up procalcitonin measurements within 1-2 days are recommended only in case of non-resolving or worsening symptoms. An increase of ≥0.25 μg/l

TABLE 1. Procalcitonin for guidance of antibiotic treatment in different clinical settings.

PCT (μg/l)	Clinical setting		
	A	B	C
<0.1	Strongly discouraged	Strongly discouraged	Empirical antibiotics strongly recommended
<0.25	Discouraged	Discouraged	
≥0.25	Encouraged	Encouraged	
>0.5	Strongly Encouraged	Strongly Encouraged	

A: Low risk patients, non-pneumonic respiratory infections, B: moderate risk, pneumonic infections in the emergency department and inpatients, C: high risk, sepsis in need of intensive care unit admission

favors the use of antibiotics. In group B patients already on antibiotics, discontinuation of antibiotic treatment is strongly encouraged for procalcitonin levels of <0.1μg/l and encouraged for levels <0.25μg/l, at follow–up. For cut off-points ≥0.25 μg/l and >0.5μg/l, discontinuation of antibiotics is discouraged and strongly discouraged respectively. In group C patients, discontinuation of antibiotic treatment is strongly encouraged if procalcitonin levels drop to <0.25 μg/l or in case of a >90% drop of the initial value at follow-up; encouraged for a cut-off point of <0.5μg/l or a >80% drop, discouraged when procalcitonin levels are ≥0.5μg/l and strongly discouraged for a cut-off point of ≥1.0μg/l. Importantly, the algorithm can be over-ruled in case of clinical instability or patients at risk of adverse outcome (immunocompromised or high PSI score).

The decline in immune function often observed in elderly patients[8-10] results in atypical and frequently subtle (e.g. mild fever or even apyrexia) clinical presentations of bacteremia[8,9,11-13], increasing the risk of under diagnosis and subsequent delays in treatment of sepsis. The usefulness of inflammatory biomarkers such as procalcitonin in older patient populations has not been adequately studied, as most previous studies included adult or pediatric patients.

In a recent meta-analysis of four studies[14-18] with a total of 760 patients, aged 65 years and older, Lee et al,[19] evaluated the diagnostic accuracy of procalcitonin for the identification of systemic bacterial infections in elderly patients.

The results showed that, **procalcitonin test** is both **specific** and **sensitive** in the diagnosis of severe bacterial infection in elderly patients while **leukocytosis** is a **specific** (Specificity: 0.86), but **poorly sensitive** (Sensitivity: 0.26) biomarker and **CRP** test is **highly sensitive** (Sensitivity: 0.91) but **non-specific** (Specificity: 0.36) test. The pooled specificity and sensitivity for the procalcitonin test was 0.83 and 0.83, respectively. While the test's positive likelihood ratio of 4.77 is not considered to be sufficiently high, it's negative likelihood ratio of 0.20 suggests a low posttest probability for a negative result in populations with a low prevalence of sepsis making it a useful rule-out diagnostic tool.

A previous meta-analysis and systematic review of procalcitonin as a bacteremia biomarker in normal adult populations by Simon et al,[20] showed a similar sensitivity (0.76, 95% CI: 0.66–0.84) and specificity (0.70, 95% CI: 0.60–0.79) to the present study, and thus, comparison of the two meta-analyses does not provide evidence of immune senescence for the procalcitonin test in elderly patients.

In conclusion, procalcitonin test, as a biomarker of bacterial infection has not been shown to have an inferior performance in elderly populations, may be useful for ruling out sepsis in low prevalence populations, but test results should be interpreted in the context of clinical findings.

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