



Infection or not infection, that is the question— Is procalcitonin the answer?

Two ongoing challenges in managing patients with a potential or real infection are how to distinguish early on between bacterial infection and sterile inflammation or sepsis syndrome and how to determine the optimal duration of antibiotic therapy. Both have implications for the patient—ie, starting appropriate antibiotic or alternative therapy early and avoiding adverse effects of unnecessarily prolonged antibiotic use—but also for society, particularly by limiting unnecessary antibiotic use, which contributes to the worldwide problem of antibiotic resistance.

Diagnostic algorithms have been proposed to help recognize infection in chronic obstructive pulmonary disease, rhinosinusitis syndrome, acute arthritis, pharyngitis, and possible sepsis. The algorithms have included laboratory tests and potential biomarkers, but all are imperfect despite achieving various degrees of acceptance in practice.

In this issue of the *Journal* (page 307), Dr. Fakheri updates us on using the data on serum procalcitonin levels to guide starting and stopping antibiotics in different clinical scenarios. As I read the paper, I wondered what was different about procalcitonin that might allow it to succeed where seemingly similar biomarkers like C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) have failed.

Procalcitonin is the approximately 15,000-kD product of the *CALC1* gene and the precursor of calcitonin. Not surprisingly, then, it is increased in patients with thyroid medullary carcinoma, and it is also often elevated in nonthyroid neuroendocrine malignancies. Proteolytic cleavage of procalcitonin to active calcitonin takes place mainly or only in the thyroid, and under normal homeostatic conditions, procalcitonin is almost unmeasurable in the circulation. However, under major stress such as systemic inflammation, sepsis, or burns, the *CALC1* gene is activated in parenchymal cells in many organs, and procalcitonin is synthesized and released. Notably, under these conditions, the procalcitonin does not seem to be of thyroid origin; hence, calcitonin levels do not rise markedly. The physiologic role of nonthyroidal procalcitonin is unknown.

Procalcitonin synthesis and secretion is turned on in nonthyroid tissue by multiple cytokines; the cytokines most likely relevant to its association with inflammation and infections are interleukin (IL) 1 beta, tumor necrosis factor (TNF) alpha, and IL-6. Since these same mediators drive the acute-phase response and elicit the increase in circulating CRP and fibrinogen (the major contributor to the ESR), the obvious question is why procalcitonin might be a more reliable biomarker to distinguish bacterial infection from inflammation or a viral infection than the CRP level or ESR. And although it does indeed seem to do so in several conditions, as Dr. Fakheri discusses, the explanation is not obvious. But it is intriguing to hypothesize.

Induction of procalcitonin by endotoxin-stimulated cytokines is rapid and seems to be slightly faster than that of CRP, although there may be issues of assay sensitivity.

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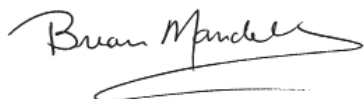
The half-life of procalcitonin is similar to that of CRP (about 24 hours). Its degradation does not seem to be altered in renal insufficiency, and its synthesis seems to rapidly shut off as the cytokine level drops. But interestingly, and perhaps relevant to its possible unique biomarker behavior, its synthesis seems to depend on factors other than the increase in inflammatory cytokines such as IL-6. Under certain circumstances, in the same patient, there is a discrepancy between the levels of procalcitonin and CRP.

In a small study of patients with pulmonary embolism and fever, IL-6 levels increased in many with an expected accompanying increase in CRP and ESR, but procalcitonin did not markedly rise,¹ although all 3 markers rose as expected in patients with bacterial pneumonia.

Even more provocative is another study in 69 patients with systemic lupus erythematosus and bacterial infection (43 patients had sepsis, 11 of whom died). The CRP level rose dramatically in the infected patients, but procalcitonin did not.²

The intriguing aspect of this, assuming it holds true in other studies, is that interferon activity is high in lupus and many viral infections, and if interferon can suppress *CALC1* gene activation³ but leave CRP activation unaffected, this may provide a clue as to why CRP but not procalcitonin is elevated in serious viral infections, thus allowing procalcitonin to more effectively distinguish bacterial from viral and other nonbacterial inflammatory responses.

The two studies I mention are small, some conflicting results have been published, and the results cannot yet be generalized. Plus, it has long been recognized there is sometimes discordance in a given patient between the elevation in ESR and CRP, not readily explained by the presence of a paraprotein, rheologic factors, or the different time course of decay in the ESR and CRP response. Whatever the explanation, procalcitonin's biology is interesting, and clinical study results show promise. While tracking procalcitonin levels is not uniformly useful (eg, there is no convincing value in using procalcitonin in the diagnosis of prosthetic joint infections), there is accumulating evidence that it can guide us to using shorter but still effective courses of antibiotics in several clinical scenarios. Hopefully, more frequent use of the test will make a dent in our apparent excess use of antibiotics in patients with nonbacterial upper-respiratory infections.



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