

# Should procalcitonin levels guide initiation of antibiotics in intensive care?

**P**rocalcitonin is a peptide precursor of calcitonin, normally present at very low levels in the plasma of healthy individuals. As an acute phase protein, its plasma levels rise in inflammatory states. Procalcitonin has a relative specificity for bacterial infections compared to viral or non-infectious inflammation (Schuetz et al, 2017). Procalcitonin levels are used to guide discontinuation of antibiotics on the intensive care unit with reduced antibiotic exposure and potential reduced antibiotic-associated side effects (Rhodes et al, 2017).

What remains more controversial is the use of procalcitonin concentrations to guide initiation of antibiotics in a patient who may or may not have an acute bacterial infection. These diagnostic dilemmas occur commonly on the intensive care unit: for example a patient who becomes febrile after an out-of-hospital cardiac arrest or a patient with acute severe pancreatitis.

## Procalcitonin levels can guide initiation of antibiotic therapy

There is concern about the inappropriate use of broad spectrum antibiotics because of increasing antimicrobial resistance. Consequently, many have examined whether procalcitonin concentrations can be used safely to prevent inappropriate initiation of antibiotic therapy.

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Much of the evidence is summarized in a Cochrane meta-analysis focusing on respiratory tract infections in primary and secondary care (Schuetz et al, 2017). Twenty six prospective randomized controlled trials of adults were included comparing use of a procalcitonin-guided algorithm for antibiotic initiation or discontinuation with standard care. Use of this algorithm significantly reduced 30-day mortality, antibiotic exposure and antibiotic-related side effects. These benefits were confirmed in a second meta-analysis of eleven randomized controlled trials in critically unwell patients with diverse infectious aetiologies (Wirz et al, 2018).

However, the differing methodologies used in these trials (some used an algorithm to initiate and discontinue antibiotic therapy, and some just to discontinue) make it difficult to establish the specific contribution of using procalcitonin to guide initiation of antibiotic therapy from the overall benefit.

## Procalcitonin levels should not guide initiation of antibiotic therapy

Many clinicians have concerns about over-reliance on biomarkers, such as procalcitonin, to guide antibiotic initiation. A false positive leads to unnecessary antibiotic initiation, exposing the patient to the risk of antibiotic-associated complications or development of resistant organisms. A false negative result could be even more harmful, leading to inappropriate delay in antibiotic initiation and increased mortality (Rhodes et al, 2017).

Using a procalcitonin cut off of 0.5 ng/ml, a meta-analysis of intensive care patients showed a pooled sensitivity of 89% and specificity of 68% for predicting bacteraemia (positive blood cultures) (Hoeboer et al, 2015). Procalcitonin as a biomarker failed to identify bacteraemia in 11% of critically unwell patients.

This meta-analysis used confirmed bacteraemia to establish a bacterial aetiology of infection, but many patients with serious bacterial infection do not develop bacteraemia. A randomized controlled trial used retrospective expert clinical opinion to confirm bacterial infection (using all available observations,

microbiology, tests and radiology) (Layios et al, 2012). Using a procalcitonin cut off of >1 ng/ml, 33.8% of patients with a positive procalcitonin test did not have a bacterial infection when scrutinised by expert clinical opinion (66.2% specificity). Using a different procalcitonin cut off (<0.25 ng/ml), 14.9% of patients with a negative procalcitonin test were deemed to have a bacterial infection on expert clinical opinion (85.1% sensitivity).

## Conclusions

The authors believe that the risk of not administering antibiotics in a critically unwell patient with possible bacterial infection greatly outweighs potential benefits. There is doubt over the suitability of procalcitonin as a biomarker to accurately guide initiation of antibiotics in intensive care patients. The authors recommend that procalcitonin levels should not routinely be used to guide initiation of antibiotics in critically unwell adults. **BJHM**

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