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Minimum repeat intervals for procalcitonin and C-reactive protein

Procalcitonin

Kinetics[1]

Procalcitonin (PCT) is a 116 amino acid peptide precursor of calcitonin. In the absence of infection, it is produced at very low levels in a few highly selected tissues. However, at the onset of infection bacterial factors and host inflammatory cytokines induce the expression of PCT in many different tissues. This results in a rapid rise in PCT levels from virtually undetectable (< 0.05ng/L) to detectable levels within 2-4 hours. Peak levels occur at 24-48 hours and the degree of the rise correlates with the severity of the systemic inflammatory response. Viral infections, localised bacterial infections and non-infectious causes of systemic inflammation do not induce high levels of PCT. Procalcitonin has a half-life of approximately 25-30 hours, which is short in comparison to other acute phase reactants. It is largely degraded by proteolysis with a minor renal excretion component.

Use as a biomarker

Procalcitonin can be used as a biomarker[2]

- for the diagnosis of sepsis, severe sepsis and septic shock
- to assess the severity of inflammation mainly induced by microbial infection
- to guide the duration of antibiotic therapy in individual patients

In severely ill ICU patients the imperfect sensitivity of procalcitonin (about 70% - 80%) means that it cannot be used as a rule-out test and initial antibiotic therapy should be given regardless of a negative result[3]. Persistently normal procalcitonin levels over time make a systemic bacterial infection very unlikely. In patients with non-severe infections, e.g. lower respiratory tract infections in patients in the community, a negative result suggests a viral cause and can therefore guide decisions on withholding antibiotics.

A recent multi-centre randomised controlled trial, The Stop Antibiotics on Procalcitonin guidance Study (SAPS)[5] conducted in ICU patients in the Netherlands, showed that a procalcitonin guidance algorithm (with non-binding advice on stopping of antibiotics) significantly reduced mortality (from 25% to 20% at 1 month and from 41% to 35% at 1 year) as well as reducing antibiotic exposure (median antibiotic consumption reduced from 9.3 defined daily doses (DDDs) to 7.5 DDDs, and median antibiotic duration reduced from 7 days to 5 days). Remarkably this decrease occurred in a healthcare system with comparatively low antibiotic consumption.

For patients with respiratory infections, a patient-level meta-analysis[6] of 26 trials in 12 countries showed significantly reduced mortality at 30 days and significantly reduced antibiotic exposure. The findings were consistent across different settings (primary care, emergency departments and ICUs) and for different types of infections. Decreases in antibiotic exposure in primary health care setting were chiefly due to not starting antibiotics whereas in ICU it was due to earlier discontinuation. Both factors played a role in decreasing antibiotic exposure in patients seen in emergency departments.

Frequency of testing

Given its half-life the maximum recommended frequency of PCT measurements is once daily[8] in critically ill ICU patients. Of note, renal impairment reduces clearance and therefore the decline in PCT may be slower in septic patients with associated renal impairment.

The only indication for repeating PCT in less than 24 hours would be in moderately ill patients e.g. patients hospitalised with pneumonia, in whom antibiotics are withheld based on an initial negative result. In such patients it is recommended that PCT should be repeated in 6-12 hours together with clinical re-assessment.

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C-reactive protein

CRP or C-reactive protein is one of the acute phase proteins[1], produced in the liver in response to release of cytokines from inflammatory cells. CRP acts as a pattern recognition molecule assisting the innate immune system in various pathways. CRP is useful in that an increase generally reflects the presence and intensity of an inflammatory process. However, it is not specific for infection and can't distinguish non-infectious causes from infectious causes, nor bacterial from non-bacterial causes.

Indications for use

- As a diagnostic test some value in distinguishing bacterial infections
- Limited value in patients who are going to be given antibiotics regardless of the result.
- Monitoring test in patients with proven bacterial infections requiring long term therapy, where clinical response alone is insufficient for determining duration of therapy, e.g. endocarditis, osteomyelitis, sometimes even TB. Occasionally a baseline reading may be useful in these situations.
- In rheumatological conditions helps to distinguish inflammatory from non-inflammatory joint pain and as a monitoring test in certain rheumatological conditions
- Ultrasensitive CRP is used in some situations for predicting risk in cardiovascular disease

Frequency of testing

Since CRP rises and falls more slowly than PCT, and since the degree of increase in CRP is not correlated with severity of infection, CRP should not be repeated more frequently than every 48 hours [2 3] (with the exception of neonates where it can be repeated every 24 hours)[4].

In a UK study[5] implementation of a 48-hour minimum repeat interval for CRP testing successfully reduced laboratory costs and also altered clinician test-requesting behaviour towards more appropriate requesting. Clinicians could motivate for more frequent testing through consultation with a consultant microbiologist (available on 24-hour basis), but only a small fraction (<3%) of such requests were approved.

References

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