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Impact of Procalcitonin Measurement on Antibiotic Administration

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Procalcitonin (PCT) is a biomarker which is used extensively, both as a surrogate marker to distinguish bacterial infections from other causes of infection (such as viral infections), and to distinguish sepsis from other causes of systemic inflammatory response syndrome (SIRS), especially in the intensive care setting (Kibe et al. 2011; Uzzan et al. 2006). Serum PCT levels have also been shown to have prognostic value in critically ill patients; particularly in patients with severe sepsis and multi-organ failure (Jensen et al. 2006). However, as with other prognostic methods such as APACHE and SOFA scores, it does not add much to clinical decision making at the bedside, but rather it is useful for research purposes. In addition, a rising PCT level may suggest that the patient is not improving in terms of the infectious problem and he or she requires further source control or meticulous control of the infectious condition.

Diagnostic Value of PCT

Although there are conflicting results, PCT has shown to be a reasonably good diagnostic marker for sepsis syndromes in the intensive care setting (Uzzan et al. 2006). The American College of Critical Care Medicine and Infectious Diseases Society of America have recommended that serum PCT levels can be used as an adjunctive diagnostic tool for discriminating infection as the cause of fever or as a tool for the diagnosis of sepsis, grading the evidence as level two (O'Grady et al. 2008). Since PCT is also elevated in non-infectious conditions, its main role is to rule out infection in cases where levels are too low. In addition, repeated measurements are more useful since basal PCT levels may be low early in the course of infection.

The utility of PCT levels to improve the early diagnosis of ventilator-associated pneumonia (VAP) has also been evaluated in some studies. Ramirez et al, (2008) reported a cohort study with sequential measurement of PCT in patients with VAP. The results of this study showed that PCT levels were statistically higher in patients with confirmed VAP. The combination of the simplified clinical pulmonary infection score (CPIS) and serum PCT had a 100 percent specificity excluding all falsepositive diagnosis of VAP.

PCT has also been studied in acute exacerbations of chronic obstructive pulmonary disease (COPD) in the differentiation of bacterial from other causes. COPD exacerbations not only increase mortality in patients, but also impose great burdens on medical resources. An estimated 50 – 75 percent of expenditures are due to COPD disease. Determination of etiologic reasons in COPD exacerbations pose a great challenge to the

clinician. Since it is difficult to determine the exact cause and especially the bacterial pathogen, almost all patients with acute exacerbations receive antibiotics empirically. Exposure to antibiotics not only increases the cost but also increase toxicity, antibiotic resistance, etc. Therefore, it is very important to differentiate bacterial causes from others.

Several studies address this issue, and reveal that a PCT value < 0.1 mcg/L on admission and on follow-up excluded the presence of bacterial infection (Daubin et al. 2009). We have conducted a similar study in our unit to determine the role of PCT in identifying the presence of bacterial infections in COPD exacerbations requiring mechanical ventilation. We studied 63 patients with a median age of 71 years. We found a negative predictive value of 89 percent for PCT if admission and follow up values are < 0.25 mcg/L (Topeli and Ergan-Arsava 2010).

Value of PCT in Antibiotherapy Plan at the Bedside

Antibiotic stewardship at the bedside is probably the most important area where PCT is useful. One of the most important challenges the intensivist faces is ICU-acquired infections due to multidrug resistant pathogens. There is a clear association between antibiotic exposure and development of resistance. Therefore current strategies advocate less antibiotic consumption. However, with this approach intensivists face the risk of causing resistance by using perhaps unnecessary antibiotics on one hand and on the other hand they might put their patients at risk of sepsis or unresolved infection by avoiding antibiotics. Therefore use of PCT in antibiotic stewardship has become a very popular subject in the last few years.
In a randomised study, Nobre et al. (2008) showed that patients with sepsis assigned to PCT-guided antibiotic treatment groups had a duration of four days of antibiotic therapy and a two-day shorter length of stay in the ICU with a similar mortality and infection recurrence rate compared to a standard care group. A recent multi-centre randomised trial (PRORATA trial) revealed that critically ill patients whose antibiotherapy was managed according to baseline and follow-up PCT levels had shorter days without antibiotics (about two - three days) than patients who received the usual care (Lila Bouadma et al. 2010). No increase in mortality and emergence of resistance were observed. Unfortunately, cost-effectiveness analysis was not performed.

Despite this, some may argue that the antibiotherapy duration in the control group is somewhat longer than some recent findings in studies, where a shorter course of antibiotherapy (such as eight days) was found to be as effective as longer duration (with the exception of infections due to Pseudomonas) (Chastre et al. 2003). However, clinicans need individualised strategies rather than fixed empirical ones. Therefore, PCT should still be regarded as one of the key markers among several clues in decision- making, and it should not be accepted as a single definite marker in determining antibiotic duration. Among several randomised controlled studies, repeated PCT measurements were used and antibiotic treatment has been discouraged when levels are <0.25-0.5 mcg/L and encouraged if levels are >0.5-1 mcg/L. In addition, recommendations for discontinuing antibiotics were made if PCT levels dropped to a range of less than 0.25-1.00 mcg/L or by at least 80 - 90 percent. PCT based algorithms reduced antibiotic treatment by about two days (Lila Bouadma et al. 2010; Hochreiter et al. 2009; Petros Kopterides et al. 2010; Schuetz et al. 2011).

PCT is also considered to be a useful tool for the determination of antibiotic treatment duration both in pneumonia and in exacerbations of COPD (Blasi et al. 2010). Schuetz et al. (2009), revealed that patients who received PCT guided treatment in lower respiratory tract infections including COPD exacerbations and community acquired pneumonia had less antibiotic exposure without any adverse outcome. Stolz et al (2007) showed that PCT guided therapy resulted in less antibiotic exposure in patients with COPD exacerbations and interestingly this reduction in total antibiotic exposure persisted for up to six months. PCT guided therapy might also be promising in ventilator associated pneumonia (Stolz et al. 2009).

Cost-Effectiveness of PCT

There is no study addressing the costeffectiveness of PCT use in antibiotic therapy directly. Schroder et al. (2009) found that the cost of antibiotic treatment was significantly reduced in the PCT-guided group compared with the control group. Heyland et al. (2011), performed a systematic review of five randomised controlled studies including the above mentioned study in critically ill patients. First, they found that based on these studies a PCT guided strategy was associated with a reduced antibiotic use by about two days. Since this

strategy did not increase mortality or length of stay and did not cause recurrence or relapses in infection, the cost model based on these findings revealed a reduction in cost of care.

Conclusions

In summary, while accepting its limitations, the technique of procalcitonin levels measurement for antibiotic administration decisions in patients with respiratory tract infections and sepsis appears to reduce antibiotic exposure without worsening the outcome. In addition, trends in its repeated measurements might give prognostic information as to whether PCT might also be useful as an adjunctive parameter for the diagnosis of bacterial infections in case of fever, or lower respiratory tract infections including COPD exacerbations in critically ill patients.

Repeated PCT measurements might also help to identify whether the patient is responding to treatment or needs further infection management. Given the fact that it might shorten length of ICU stay and antibiotic usage for up to six months in COPD, PCT guided antibiotic therapy may also be considered as cost-effective. However, further studies are needed to determine the following:

- Cut-off values in different disease settings;
- Effectiveness in antibiotic stewardship in ICU acquired infections due to multi-drug resistant microorganisms, and
- Its cost-effectiveness comparing PCT guided therapy with a control group who received relatively shorter duration of antibiotics than conventional 10 - 14 days of therapy or with cheaper markers such as CRP guided therapy (Shehabi et al. 2008).

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