Journal club critique

Procalcitonin-guided antibiotics in severe sepsis

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Expanded Abstract

Citation

Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J: Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008, 177: 498–505 [1].

Background

The duration of antibiotic therapy in critically ill patients with sepsis can result in antibiotic overuse, increasing the risk of developing bacterial resistance. Procalcitonin (PCT)-guided antibiotic use reduces antibiotic exposure in community-acquired pneumonia. Whether it might also reduce antibiotic exposure in severe sepsis is unknown.

Methods

Objective

To test the hypothesis that an algorithm based on serial measurements of PCT allows reduction in the duration of antibiotic therapy compared with empirical rules, and does not result in more adverse outcomes in patients with severe sepsis and septic shock.

Design

Single-center, non-blinded randomized controlled trial.

Setting

Mixed medical and surgical ICU at a university teaching hospital.

Subjects

79 adult patients with suspected severe sepsis or septic shock.

Intervention

All patients had circulating PCT levels drawn daily. In patients randomly assigned to the intervention group, antibiotics were stopped when PCT levels had decreased 90% or more from the initial value (if clinicians agreed) but not before Day 3 (if baseline PCT levels were <1 mg/L) or Day 5 (if baseline PCT levels were >1 mg/L). In control patients, clinicians decided on the duration of antibiotic therapy based on empirical rules.

Outcome

Systemic antibiotic exposure, measured using three variables: 1) duration of antibiotic treatment, 2) antibiotic exposure days per 1000 inpatient days, and 3) days alive without antibiotics within the 28-day follow-up period.

Results

Patients assigned to the PCT group had 3.5-day shorter median duration of antibiotic therapy for the first episode of infection than control subjects (intention-to-treat, n = 79, P = 0.15). In patients in whom a decision could be taken based on serial PCT measurements, PCT guidance resulted in a 4-day reduction in the duration of antibiotic therapy (per protocol, n = 68, P = 0.003) and a smaller overall antibiotic exposure (P = 0.0002). A similar mortality and recurrence of the primary infection were observed in PCT and control groups. A 2-day shorter intensive care unit stay was also observed in patients assigned to the PCT group (P = 0.03).

Conclusion

Our results suggest that a protocol based on serial PCT measurement allows reducing antibiotic treatment duration and exposure in patients with severe sepsis and septic shock without apparent harm.

Commentary

Procalcitonin (PCT), the biologically active precursor of the calcium-modulating hormone calcitonin [2], has been shown in diverse studies to be closely associated with the human

host response to bacterial infection [3-6]. It is elaborated by parenchymal cells throughout the body in response to endotoxin and several pro-inflammatory mediators (in particular TNF-α) and its concentration appears to be roughly linear with the degree of insult [7]. The use of circulating PCT measurement to guide antibiotic therapy reduces antibiotic exposure in patients with suspected lower respiratory tract infection in both the inpatient and outpatient setting [8-10]. The role of PCT in patients with more severe infections such as severe sepsis has yet to be fully elucidated, but it has tantalizing performance characteristics as a biomarker for bacterial infection, showing diagnostic superiority to white cell count, C-reactive protein, and a host of physiologic variables in most reports [11]. However, these investigations suffer from the absence of a diagnostic gold-standard, a common problem in studies of infection [12]. The use of PCT to diagnose bacteremia or sepsis has been the subject of significant debate and at least three meta-analyses, two supporting [13,14] and one discouraging [15] its clinical utility.

In the present single-center randomized controlled trial the authors evaluated a protocol for antibiotic cessation based almost entirely on plasma PCT level, with the primary outcome relating to the duration of antibiotic exposure. Seventy-nine intensive care unit (ICU) patients with suspected severe sepsis or septic shock according to ACCP-SCCM consensus criteria [16] were randomized to either usual care or a protocol arm in which the duration of antibiotics was determined by serial PCT measurements. These patients were quite ill, with ~50% requiring vasopressors and ~80% invasive ventilation. Serum PCT measurements were obtained daily and antibiotic cessation was encouraged on either day 3 or day 5 (depending on the initial PCT level) in intervention patients who experienced a predefined relative or absolute decline in PCT, with the implicit assumption that these patients had resolved their septic focus. The intention-to-treat analysis showed a nonsignificant trend toward reduced duration of antibiotics use. In the per-protocol analysis, PCT-guided therapy not only resulted in significant decreases in duration of antibiotic use, but a 2-day shorter ICU stay. Mortality and infection recurrence rates were similar between groups.

This study does have significant appeal. Rather than focusing on whether PCT can accurately diagnose infection, the authors have instead shown that it can be used as part of a treatment protocol to reduce antibiotic duration in some of the sickest ICU patients. The study does, however, have limitations that deserve consideration. Important exclusion criteria included the presence of certain difficult to eradicate pathogens (notably, *Pseudomonas aeruginosa* and *Acinetobacter baumanni*), infections requiring prolonged antibiotic therapy (e.g., endocarditis, deep abscesses) and immunosuppressed subjects, such as those with human immunodeficiency virus, neutropenia, or solid organ transplantation. The ultrasensitive PCT assay used in the study is not yet widely available. Even the standard PCT assay has a turn-around time measured in days, rather than hours, in many academic medical centers, such as our own where PCT is a "send out" lab. The results of the study were only significant in the per-protocol analysis, which was limited to patients with several days of follow-up and without post-randomization death or diagnosis of complicated infection requiring extended antibiotic therapy. This was designed to limit the analysis to subjects in whom a decision to stop antibiotics could actually be taken based on PCT levels. Though this approach is not inherently wrong, the use of serial PCT levels to guide therapy requires levels to be drawn on all patients, not just those in which PCT later proves to be of benefit, which raises issues of cost-effectiveness. Even so, the positive trend seen in the intention-to-treat analysis is reassuring and may have become significant had more subjects been enrolled.

Unfortunately, the main shortcoming of the study is that it was not powered to answer the real question. That is, can antibiotic exposure be safely reduced? Mortality and infection recurrence rates were similar between groups, suggesting that antibiotic use was reduced without harming patients. Yet, as the authors point out, a study powered for these endpoints would require several hundred patients per arm.

There are several large ongoing or recently completed multicenter trials of PCT-guided antibiotic therapy in ICU patients with infection. The PROcalcitonin to Reduce Antibiotic Treatments in Acute-Ill Patients (PRORATA) study, a 630 patient study in adult ICU patients with presumed bacterial infection, completed enrollment May 2008 [17]. The Procalcitonin and Survival Study (PASS), a 1000 patient study in adult ICU patients with severe sepsis, is expected to complete enrollment in early 2009 [18]. An additional study in 200 adult ICU patients with suspected infection, but no clear-cut source by clinical or microbiological criteria, is expected to close in late 2009 [19]. [1]

Recommendation

The PCT-based protocol in the study does appear to reduce antibiotic exposure in patients with severe sepsis, but issues of assay availability, generalizeability, safety, and cost-effectiveness must be addressed before we can recommend its routine use.

Competing interests

The authors declare that they have no competing interests.

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