When once is not enough--further evidence of procalcitonin-guided antibiotic stewardship

Harbarth, Stéphan Juergen; Albrich, Werner C.; Muller, Beat

How to cite

HARBARTH, Stéphan Juergen, ALBRICH, Werner C., MULLER, Beat. When once is not enough--further evidence of procalcitonin-guided antibiotic stewardship. In: Critical care, 2009, vol. 13, n° 4, p. 165. doi: 10.1186/cc7935

This publication URL: https://archive-ouverte.unige.ch/unige:19854
Publication DOI: 10.1186/cc7935

Commentary

When once is not enough – further evidence of procalcitonin-guided antibiotic stewardship

Stephan Harbarth[1], Werner C Albrich[2] and Beat Müller[2]

[1]Infection Control Program, Department of Internal Medicine, University of Geneva Hospitals and Medical School, CH-1211 Geneva 14, Switzerland
[2]Department of Internal Medicine, Kantonsspital Aarau, CH-5001 Aarau, Switzerland

Corresponding author: Stephan Harbarth, stephan.harbarth@hcuge.ch

Published: 13 July 2009
This article is online at http://ccforum.com/content/13/4/165

Critical Care 2009, **13:**165 (doi:10.1186/cc7935)

See related research by Hochreiter *et al*., http://ccforum.com/content/13/3/R83

Abstract

Every day, critical care physicians around the world face the same challenge of the optimal timing of antimicrobial administration: when to start and when to stop antibiotics. Duration of antibiotic therapy for sepsis is mostly based on expert opinion, but its reduction is arguably the most promising approach to decrease emergence and selection of antibiotic resistance. The study by Hochreiter and colleagues presents another piece of evidence suggesting that procalcitonin may indeed be a valuable diagnostic parameter to guide antibiotic treatment duration, despite the ongoing controversy about the diagnostic accuracy of procalcitonin.

In the previous issue of *Critical Care*, Hochreiter and colleagues presented another piece of evidence suggesting that procalcitonin (PCT) may indeed be a valuable diagnostic parameter to guide antibiotic treatment duration [1].

Misuse of antimicrobial agents has been a long-lasting problem in intensive care units (ICUs). Drivers of inappropriate prescribing include diagnostic uncertainty, lack of knowledge, unavailability of microbiologic support or infectious disease specialists, pharmaceutical marketing pressure, and the overarching fear of missing a life-threatening infection. Every day, critical care physicians around the world face the same challenge of the optimal timing of antimicrobial administration: when to start and when to stop antibiotics.

The duration of antibiotic therapy for sepsis is mostly based on expert opinion [2], but its reduction is arguably the most promising approach to decrease emergence and selection of antibiotic resistance. During the past 10 years, great progress has been made to decrease the antibiotic treatment duration for various types of infections, including community-acquired pneumonia and ventilator-associated pneumonia, by implementing fixed 8-day stopping rules [3,4]. A more tailored approach could be the use of algorithms based on the longitudinal course of biomarkers to facilitate individual decision-making and choose the right moment for discontinuation of antibiotic therapy.

At the current moment, PCT represents the best studied biomarker for guiding antibiotic treatment duration in the inhospital setting. Several randomized clinical trials investigating the diagnostic performance and clinical effectiveness of PCT have been published within the past 5 years or are currently submitted for publication [5-11]; however, few of them included a sufficient number of patients with severe sepsis and septic shock. In several of these studies, ICU admission was considered an acceptable criterion to overrule the PCT-based algorithm and initiate antibiotic therapy despite low PCT levels. Nobre and colleagues have shown recently that the application of an algorithm based on PCT levels allowed significant shortening of the duration of antibiotic therapy and of the ICU stay in critically ill patients with life-threatening infections, without apparent harm to patients [10].

In their article, Hochreiter and colleagues published the English translation of another randomized clinical trial of critically ill patients with different types of infections [1], confirming the study findings by Nobre and colleagues [10]. The original version of the *Critical Care* article has already been published in German in a peer-reviewed journal [12] and the analysis of a slightly different subgroup of patients has also been reported previously [13]. The major finding of these three articles is almost identical and relates to the reduction of the average antibiotic treatment duration and length of ICU stay by about 2 days.

ICU = intensive care unit; PCT = procalcitonin.

The study by Hochreiter and colleagues was larger than previously published PCT trials conducted in the ICU setting. Some issues, however, warrant further comment. First, although it is likely that the reduction effect was mainly caused by the study intervention (PCT algorithm), it remains unclear in how many cases the PCT algorithm was forced into action by the study physicians or was overruled by the physicians in charge.

Second, the precise microbiologic etiology of the causative organisms and the documented relapse rate, secondary infections or other complications such as reoperations were not mentioned. It is conceivable that several cases of pneumonia or peritonitis were bacteremic or had a more complicated course, leading to potential antibiotic underuse and/or reintroduction at a latter time point. Given the heterogeneity of the included patients and infectious syndromes, a uniform 8-day antibiotic course for the control group might not reflect the standard of care for all indications. Indeed, it was different from the treatment approach for the control group in the previously reported subgroup analysis by the same authors, where 'treatment was discontinued according to clinical signs and empiric rules' [13].

Third, the study methods do not explain how the clinicians were blinded to the PCT values in the control arm, in order to avoid a spillover effect. How investigators were blinded for outcome assessment to avoid differential misclassification bias is also not described.

Fourth, the investigators used an insensitive PCT assay, which has been replaced in many settings by a more sensitive assay, considered more suitable for guiding antibiotic treatment decisions and for determining treatment-stopping rules [14].

Finally, it would have been interesting to know whether PCT is now implemented in their ICU as a routine parameter for the daily follow-up and how this practice influences real-life treatment decisions, outside a controlled study setting. There is potential for PCT overuse, as with all diagnostic tools, increasing expenditures due to the still-high costs of this test and unforeseen adverse consequences if used indiscriminately.

Despite these limitations, the study by Hochreiter and colleagues presents another piece of evidence suggesting that PCT may indeed be a valuable diagnostic parameter to guide antibiotic treatment duration. Seven randomized clinical trials about the diagnostic effectiveness of PCT have currently been completed [5-11], and several more are being conducted in different parts of the world, according to international trial registers (http://clinicaltrials.gov/ct2/results?term=procalcitonin). Preliminary data from some of these trials are available and confirm the safety and efficacy of PCT guidance.

In summary, all these data from randomized clinical trials are good news for ICU physicians, despite the ongoing controversy about the diagnostic accuracy of PCT [15,16]. Clearly, we need even better diagnostic decision support tools if we want to help clinicians in their daily struggle for improving antibiotic treatment decisions.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

All authors have received speaker honoraria from BRAHMS AG. SH and BM have received research support from BRAHMS AG.

References

1. Hochreiter M, Kohler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S: **Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial.** *Crit Care* 2009, **13:**R83.
2. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG: **Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults.** *Clin Infect Dis* 2007, **44(Suppl 2):**S27-S72.
3. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S for the PneumA Trial Group: **Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial.** *JAMA* 2003, **290:**2588-2598.
4. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z, Falagas ME: **Short- versus long-course antibacterial therapy for community-acquired pneumonia : a meta-analysis.** *Drugs* 2008, **68:**1841-1854.
5. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, Periat P, Bucher HC, Christ-Crain M: **Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care.** *Arch Intern Med* 2008, **168:** 2000-2007; discussion 2007-2008.
6. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Muller B: **Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial.** *Lancet* 2004, **363:**600-607.
7. Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Muller B: **Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial.** *Am J Respir Crit Care Med* 2006, **174:**84-93.
8. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, Huber P, Muller B, Tamm M: **Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy.** *Chest* 2007, **131:**9-19.
9. **Procalcitonin Reduces Antibiotic Treatments in Acute-ill Patients (PRORATA)** [http://clinicaltrials.gov/ct2/show/NCT00472667]
10. 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.
11. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, Widmer I, Neidert S, Blum CA, Schonenberger R, Henzen C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Müller B for the ProHOSP study group: **Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial.** *BMC Health Serv Res* 2007, **7:** 102.
12. Hochreiter M, Kohler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroder S: **Antibiotic treatment of surgical intensive care patients: procalcitonin to guide duration of therapy.** *Anaesthesist* 2008, **57:**571-577.
13. Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, von Spiegel T: **Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive**

care patients with severe sepsis: results of a prospective randomized study. *Langenbecks Arch Surg* 2009, **394:**221-226.
14. Nylen E, Muller B, Becker KL, Snider R: **The future diagnostic role of procalcitonin levels: the need for improved sensitivity.** *Clin Infect Dis* 2003, **36:**823-824; author reply 826-827.
15. Christ-Crain M, Muller B: **Procalcitonin in bacterial infections – hype, hope, more or less?** *Swiss Med Wkly* 2005, **135:**451-460.
16. Shehabi Y, Seppelt I: **Pro/Con debate: is procalcitonin useful for guiding antibiotic decision making in critically ill patients?** *Crit Care* 2008, **12:**211.