International Journal of Antimicrobial Agents 46 (2015) S10–S12

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Can procalcitonin monitoring reduce the length of antibiotic treatment in bloodstream infections?

Iliana-Maria Pantelidou*, Evangelos J. Giamarellos-Bourboulis

4th Department of Internal Medicine, University of Athens, Medical School, Athens, Greece

ARTICLE INFO

Keywords:
Procalcitonin
Bloodstream infections
Treatment duration

ABSTRACT

Antibiotic overconsumption and subsequent bacterial multidrug resistance are associated with increased mortality, length of hospitalisation and healthcare costs. Discontinuation of antibiotic treatment in severe infections, such as bloodstream infections (BSIs), is a demanding clinical decision. In this review, we aim to investigate the usefulness of procalcitonin (PCT) monitoring in guiding appropriate treatment duration in BSIs and its impact on clinical outcomes. Data from clinical studies conducted after 2005 that included patients with BSIs indicate that change of PCT is an early indicator for prognosis in terms of survival and, overall, support the usefulness of a PCT-guided clinical algorithm in reducing the duration of antibiotic treatment without compromising survival. Furthermore, the presented data indicate that PCT assessment is helpful in the diagnosis of infective endocarditis. In conclusion, monitoring of PCT together with evaluation of the clinical situation is a valuable tool in reducing the length of antimicrobial treatment in BSIs.

1. Introduction

Emerging bacterial resistance to multiple antimicrobial agents urges the need for more efficient strategies to reduce the use of antimicrobial agents in self-limited and non-bacterial diseases and to shorten the duration of antibiotic treatment in bacterial infections. Moreover, antibiotic consumption and acquired antimicrobial resistance have been shown to be associated with increased length of hospitalisation and increased healthcare costs [1].

Bloodstream infections (BSIs) are a significant cause of mortality. The rate of misuse of antimicrobials for treatment of BSIs has been reported to be 41–85% [2]. This results mainly from the initial 48–72-h period of empirical treatment before the antibiogram becomes available. It is evident that we are in need of techniques that provide a rapid indication for de-escalation or stopping of antimicrobial therapy. The most promising biomarker in guiding these therapeutic decisions is procalcitonin (PCT) [3].

Plasma PCT rises within 3–6 h from initial clinical manifestation of sepsis and falls when severe infection is controlled [4]. High PCT concentrations are typically found in bacterial infections, whereas lower levels predominate in viral infections, and levels <0.1 ng/mL in patients without infection [5]. BSIs are a potent stimulus for PCT production [6].

In this review, we present the results of clinical studies that aimed to decipher the role of serial PCT measurements as a tool to shorten antibiotic treatment duration.

2. Current problems in guiding antimicrobial treatment

It is well established that delay in initiation of effective antimicrobial therapy is associated with poor sepsis outcome. Kumar et al. postulated that initiation of effective antimicrobial therapy within the first hour following onset of septic shock-related hypotension was associated with 79.9% survival to hospital discharge [7]. Every additional hour delay until start of effective antimicrobial initiation was associated with a significant decrease in the chance of survival of 7.6%. However, the study also demonstrated the existence of substantial delay until start of effective antimicrobials in septic shock. More precisely, among patients who were not already receiving effective therapy, the median time to start of effective antimicrobial therapy following onset of hypotension was 6 h [7].

Most laboratories report the results of blood cultures after 24–48 h. Even in that case, microbiology diagnosis fails in >50% of patients with severe infections. Bouza et al. found that the delay until the final microbiological report becomes available is an independent risk factor for infection-related mortality [8]; the risk of death increases 1.2-fold for each day until definitive

* Corresponding author at: 4th Department of Internal Medicine, ATTIKON University Hospital, 1 Rimini Street, 12462 Athens, Greece. Tel.: +30 210 58 31 985; fax: +30 210 53 26 446.
E-mail address: I.Pantelidou@med.uoa.gr (I.-M. Pantelidou).

http://dx.doi.org/10.1016/j.ijantimicag.2015.10.005

microbiological information is available. Furthermore, ineffective empirical therapy had a dramatic impact on the presence of *Clostridium difficile*-associated diarrhoea and prolonged the length of hospital stay.

In light of the failure of pathogen detection and the increase in risk of death with the time delay of delivery of a proper microbiology report, prognosis becomes an everyday calamity with the emergence of multidrug-resistant pathogens; this leads to inappropriate empirical treatment with unpredictable outcome. In a recent study among patients with BSIs from 46 Greek hospitals conducted by Koupetori et al., the most frequent isolates for infections admitted in the emergency department were *Escherichia coli* and *Klebsiella pneumoniae* [9]. Production of extended-spectrum β-lactamases (ESBLs) during the period 2010–2013 reached 27.1% in comparison with 16.4% the previous years (2006–2009) ($P = 0.016$), and production of KPC carbapenemases increased from 7.5% to 14.8% respectively ($P = 0.031$). Reported resistance rates were far greater for patients with infections acquired after admission to the intensive care unit (ICU), reaching 75% for carbapenems.

To achieve prompt initiation of appropriate antibiotic treatment of severe infections and to eliminate needless prolonged antibiotic administration, clinical algorithms that co-evaluate PCT kinetics have been developed and shown to provide useful information.

3. The role of procalcitonin

3.1. Change of procalcitonin to inform about prognosis

Several prospective studies have tried to explore whether early change of serum PCT can advise on final outcome. This could be extrapolated as information for the appropriateness of administered antimicrobial therapy in case microbiology is not available. A prospective multicentre study by Georgopoulou et al. conducted in 15 Greek hospital departments enrolled 289 septic patients in the general ward or the ICU; 33.4% had BSIs [10]. The study showed that a decrease of serum PCT by at least 30% or its persistence at levels <0.25 ng/mL within the first 48 h since the onset of empirical antimicrobial treatment was an indicator of favourable survival outcome [odds ratio (OR) for death = 0.328, 95% confidence intervals (CI) 0.173–0.621; $P = 0.001$]. In contrast, increased or stable PCT values indicated inappropriateness of the administered antimicrobials (OR = 2.519, 95% CI 1.495–4.245; $P = 0.003$).

The importance of change of PCT as an early indicator for prognosis was confirmed by retrospective analysis of data from two independent US critical care settings by Schuetz et al. [11]. PCT kinetics within the first 72 h was found to be an accurate mortality predictor, independently of initial severity assessment. In particular, a 72-h PCT decrease >80% from baseline had a 90% negative predictive value to predict death, whereas no decrease or an increase in PCT over 72 h had a positive predictive value of 50%.

3.2. Procalcitonin can advise stopping of treatment

The efficacy of a PCT-based algorithm in comparison with standard guidelines on antibiotic use was tested in a multicentre randomised trial in emergency departments of six tertiary care hospitals in Switzerland [12]; 1359 patients with lower respiratory tract infection were enrolled. Among 925 patients with community-acquired pneumonia, 72 (7.8%) had positive blood cultures. The study endpoint was the validity of the tested algorithm to reduce antibiotic exposure without increasing the risk of adverse outcomes. PCT was measured on admission, on Days 3, 5 and 7, and at discharge. According to the PCT algorithm, initiation or continuation of antibiotics was strongly discouraged if PCT was <0.1 μg/L and was discouraged if levels were ≤0.25 μg/L; initiation or continuation of antibiotics was strongly encouraged if PCT was >0.5 μg/L and was encouraged if levels were >0.25 μg/L. The PCT algorithm was effective in reducing antibiotic exposure: the mean duration of intravenous antibiotic therapy was reduced by 17.1% ($P < 0.001$) and that of oral antibiotic therapy was reduced by 48.5% ($P < 0.001$).

In a prospective randomised study by Schroeder et al., the clinical usefulness of PCT in reducing the length of antibiotic treatment was investigated in surgical intensive care patients [13]: 27 patients with severe sepsis following abdominal surgery and simultaneous start of antibiotics were randomly assigned either to a PCT-guided treatment group ($n = 13$) or to a control group ($n = 14$). PCT was measured daily. Antimicrobials were discontinued if PCT dropped to 1 ng/mL or at least 25% of the initial value for 3 consecutive days. The duration of antibiotic treatment was 6.6 ± 1.1 days in the PCT-guided group and 8.3 ± 0.7 days in the control group ($P < 0.001$). No negative effects on outcome were observed, whereas the cost of antibiotic treatment was reduced by 17.8% ($P < 0.01$).

A second study regarding surgical patients with severe sepsis or septic shock in the ICU retrospectively analysed the effect of the implementation of a PCT-guided algorithm in antibiotic consumption, using the same PCT cut-off values [14]. Length of antibiotic therapy was reduced by an average of 1 day per year, from 14.3 ± 1.2 days in 2005 to 9.0 ± 1.7 days in 2009 ($P = 0.02$), without compromising clinical outcomes. Furthermore, this reduction was associated with a significant reduction in re-infection rate (35.1%; $P = 0.014$), length of stay in the ICU (2.7 days per year; $P < 0.001$) and ventilation hours (42 h per year; $P = 0.008$).

In contrast to the previous studies, Jensen et al. tested an escalation strategy based on daily PCT measurements in a randomised controlled open-label trial in critically ill patients in the ICU [15]: PCT levels >1 ng/mL that were not decreasing more than 10% from the previous day alerted clinicians to intensify antibiotic treatment. This algorithm led to a prolonged length of stay in the ICU and substantially higher use of broad-spectrum antimicrobials. However, these results could be due to the low microbial resistance rates of Denmark, where the study was conducted. Besides, in the subgroup of patients with verified BSIs, a shorter time to administration of appropriate antimicrobials was observed for the PCT group (0.1 days vs. 0.8 days; $P = 0.02$).

3.3. Procalcitonin in the diagnosis of infective endocarditis (IE)

PCT appears to be useful in distinguishing patients with IE, thus guiding appropriate antimicrobial treatment duration. The most recent prospective study by Knudsen et al. enrolled 759 consecutive patients with clinical suspicion of IE assessed by transoesophageal echocardiography [16]; 263 had positive blood cultures. PCT concentrations were found to be significantly higher in patients with IE ($P < 0.0005$), as opposed to C-reactive protein and erythrocyte sedimentation rate. Bacteraemia with endocarditis-typical organisms, specifically *Staphylococcus aureus*, was the strongest independent determinant of high PCT ($P < 0.001$). Nevertheless, it was not possible to identify a clinically useful PCT threshold for diagnosing or excluding IE.

A previous prospective study by Mueller et al. in 67 consecutive patients admitted to the hospital with suspicion of IE demonstrated that PCT levels were significantly higher in patients with confirmed IE compared with those with rejected IE ($P < 0.001$) [17]. Using a cut-off value of 2.3 ng/mL, PCT had an 81% sensitivity and 85% specificity in predicting IE. The authors recommended the routine use of PCT in the evaluation of patients with suspected IE in addition to the established diagnostic criteria.

Jereb et al. evaluated PCT as a diagnostic laboratory parameter in predicting IE among patients with severe infections [18]: 23 patients with IE, 30 patients with sepsis and 30 with viral

encephalitis were enrolled in a prospective study. The median serum PCT level in patients with IE was higher in comparison with those with viral encephalitis ($P < 0.001$); however, distinction between patients with sepsis and those with IE solely on the basis of PCT concentration was not possible. The highest PCT levels were found in the group of patients with *S. aureus* endocarditis ($P = 0.009$). Interestingly, median PCT levels were significantly higher among patients with native valve endocarditis than among patients with prosthetic valve endocarditis ($P = 0.002$).

The specificity of PCT in relation to the causative pathogen of IE has also been confirmed in a prospective analysis by Cuculi et al., who enrolled 77 patients with suspected IE [19]. PCT was significantly elevated among patients with *S. aureus* endocarditis compared with IE due to other pathogens ($P = 0.029$), concluding that PCT has the potential to be used in the early diagnosis of *S. aureus* endocarditis.

4. Conclusion

Monitoring of PCT is a valuable tool for guiding therapeutic decisions regarding the length of antimicrobial treatment. This strategy contributes to less extensive antibiotic treatment with positive effects on the development of microbial drug resistance as well as on health economics. However, adequate interpretation of PCT concentrations always requires the evaluation of the clinical presentation.

Funding: BRAHMS GmbH.

Competing interests: None declared.

Ethical approval: Not required.

References

[1] Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis 2006;42(Suppl 2):S82–9.

[2] Elhanan G, Sarhat M, Raz R. Empiric antibiotic treatment and the misuse of culture results and antibiotic sensitivities in patients with community-acquired bacteraemia due to urinary tract infection. J Infect 1997;35:283–8.

[3] Carrol ED, Thomson AP, Hart CA. Procalcitonin as a marker of sepsis. Int J Antimicrob Agents 2002;20:1–9.

[4] Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Muller B. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. Crit Care Med 2004;32:1715–21.

[5] Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515–8.

[6] Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med 2011;171:1322–31.

[7] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.

[8] Bouza E, Sousa D, Muñoz P, Rodríguez-Créixems M, Fron C, Lechuz JG. Bloodstream infections: a trial of the impact of different methods of reporting positive blood culture results. Clin Infect Dis 2004;39:1161–9.

[9] Koupetori M, Retsas T, Antonakos N, Vlachogiannis G, Perdios I, Nathanail C, et al. Bloodstream infections and sepsis in Greece: over-time change of epidemiology and impact of de-escalation on final outcome. BMC Infect Dis 2014;14:272.

[10] Georgopoulou AP, Savva A, Giamarellos-Bourboulis EJ, Georgitsi M, Raftogiannis M, Antonakos N, et al. Early changes of procalcitonin may advise about prognosis and appropriateness of antimicrobial therapy in sepsis. J Crit Care 2011;26, 331.e1–7.

[11] Schuetz P, Maurer P, Punjabi V, Desai A, Amin DN, Gluck E. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. Crit Care 2013;17:R115.

[12] Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;302:1059–66.

[13] Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, et al. 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;394:221–6.

[14] Hohn A, Schroeder S, Gehrt A, Bernhardt K, Bein B, Wegscheider K, et al. Procalcitonin-guided algorithm to reduce length of antibiotic therapy in patients with severe sepsis and septic shock. BMC Infect Dis 2013;13:158.

[15] Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011;39:2048–58.

[16] Knudsen JB, Fuursted K, Petersen E, Wierup P, Mølgaard H, Poulsen SH, et al. Procalcitonin in 759 patients clinically suspected of infective endocarditis. Am J Med 2010;123:1121–7.

[17] Mueller C, Huber P, Laifer G, Mueller B, Perruchoud AP. Procalcitonin and the early diagnosis of infective endocarditis. Circulation 2004;109:1707–10.

[18] Jereb M, Kotar T, Jurca T, Lejko Zupanc T. Usefulness of procalcitonin for diagnosis of infective endocarditis. Intern Emerg Med 2009;4:221–6.

[19] Cuculi F, Toggweiler S, Auer M, der Maur ChA, Zuber M, Erne P. Serum procalcitonin has the potential to identify *Staphylococcus aureus* endocarditis. Eur J Clin Microbiol Infect Dis 2008;27:1145–9.