J Korean Med Sci. 2019 Apr 15;34(14):e122
https://doi.org/10.3346/jkms.2019.34.e122
eISSN 1598-6357·pISSN 1011-8934

JKMS

Editorial

Procalcitonin to Guide Antibiotic Therapy for Critically Ill Patients in Korea

Seong Yeon Park

Department of Infectious Diseases, Dongguk University Ilsan Hospital, Goyang, Korea

▸ See the article "Procalcitonin-Guided Treatment on Duration of Antibiotic Therapy and Cost in Septic Patients (PRODA): a Multi-Center Randomized Controlled Trial" in volume 34, number 14, e110.

Received: Apr 11, 2019
Accepted: Apr 11, 2019

Address for Correspondence:
Seong Yeon Park, MD
Department of Infectious Diseases, Dongguk University Ilsan Hospital, 27 Dongguk-ro, Ilsandong-gu, Goyang 10326, Republic of Korea.
E-mail: psy99ch@hanmail.net

ORCID iDs
Seong Yeon Park
https://orcid.org/0000-0001-8762-7006

Disclosure
The author has no potential conflicts of interest to disclose.

Unnecessary antibiotic use, as a consequence of sepsis over-diagnosis, is associated with increased length of stay, drug-related toxicities, *Clostridioides difficile* infection, antimicrobial resistance, and healthcare costs.[1] However, the lack of a gold standard diagnostic test for sepsis has resulted in diagnostic dilemmas that clinicians are reluctant to withhold antibiotics when infection is suspected. Subsequent antibiotic de-escalation can be challenging because less than half of patients with sepsis never have a pathogen identified. Therefore, the use of novel biomarkers to improve the accuracy and early diagnosis of sepsis is an attractive strategy.

Among sepsis biomarkers, procalcitonin (PCT), a precursor of calcitonin, has been most widely studied to guide antibiotic prescription in septic patients.[2-4] PCT is undetectable in healthy states, but it is stimulated synergistically by the inflammatory mediators of host response, bacterial products, and necrotic body cells.[5] Serum PCT levels rise rapidly in response to systemic inflammatory insults, with peak levels that correlated with the intensity of the stimulus. PCT has a short half-life (25–30 hours), and its levels decline rapidly with a resolution of inflammation.[6] Those properties make it potentially useful in helping decide whether to stop antibiotics and when to stop antibiotics in clinically improving patients.

The first large multicenter study, PROcalcitonin Reduce Antibiotic Treatments in Acute-Ill Patients trial was conducted in France and included 621 adult patients with suspected bacterial infection in the intensive care unit (ICU).[3] The cut off PCT value for discontinuation was < 0.5 ug/L or a decrease from peak value by ≥ 80%. The PCT group had an overall 23% relative reduction in days of antibiotic exposure with noninferiority for 28-day and 60-day mortality. The largest randomized trial to date was the Stop Antibiotics on guidance of Procalcitonin Study, patients with suspected infection admitted to the ICU in the Netherlands.[2] The PCT group had a significantly lower median antibiotic daily dose and days of treatment. In addition, PCT group had significantly lower mortality at 28 days and at 1 year.

Herein, a prospective, randomized, controlled trial was performed by Jeon et al.[7] to assess the efficacy and safety of using PCT to guide antibiotic duration in the Korean ICU setting.[7] From 4 sites in South Korea, 62 adult patients admitted to the ICU with presumed or proven infection were enrolled. Patients received standard of care versus PCT-guided

antibiotic discontinuation. For the PCT group, antibiotic discontinuation was advised if PCT concentration has decreased by 80% or more of its peak value or when it reached a value of 0.5 ug/L or lower.[2,3] Median duration of antibiotic treatment for sepsis was 4 days shorter in the PCT group, and PCT-guided therapy decreased antibiotic cost by $30. However, antibiotics were stopped of this advice for only 48% patients and the number of enrolled patients was small. Despite these limitations, this article has some important clinical implications. First, this study is performed in South Korea, in non-European country. European county, such as the Netherlands, a country known to have judicious antibiotic prescribing practices and a low prevalence of antimicrobial resistance compared to the Asian country. This study showed that PCT-guided antibiotic discontinuation in patients with sepsis could reduce the duration of antibiotic use in a country with a high prevalence of antimicrobial resistance, such as South Korea. Second, they performed a cost-effectiveness analysis of PCT-guided antibiotic therapy, and PCT-guided therapy decreased antibiotic costs. The considerable cost of PCT testing remained an important barrier to broader implementation. However, this finding added evidence for PCT testing for sepsis might be cost-effective, and PCT testing for sepsis management has been reimbursed by the National Health Insurance Service of Korea based on the result of the present study.

Despite the strength of evidence described above,[2,3,7] there are a few limitations to these studies that clinicians should be aware of before using PCT in practice.[8] First, protocol adherence in the ICU based trials has been approximately 50%.[2,3,7] How closely physicians outside of clinical trials adhere to evidence-based algorithms is unclear. Second, previous studies used different cutoff values. In the ICU setting, values of 0.1, 0.25, 0.5,[2-4] and as high as 2 ug/L were used.[1] The lack of agreement on a universally accepted cut-off has reduced clinician's confidence and led to poor protocol compliance with study protocol. Therefore, future studies are required to explore the comparative effectiveness of different algorithms to optimize the use of PCT. Third, clinicians should be aware that immunocompromised patients have been generally excluded from trials. Finally, clinicians must remember that PCT can have false positive (i.e., following surgery, trauma, shock, burns) and false negative, which can occur in localized infection or the early stages of systemic infection. Although far from being a perfect marker, PCT is one of the best, and it is certainly the most widely studied. When used properly as a clinical decision aid, the evidence is robust that PCT could be a useful antibiotic stewardship tool.

REFERENCES

1. 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(15):1322-31.
PUBMED | CROSSREF
2. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016;16(7):819-27.
PUBMED | CROSSREF
3. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;375(9713):463-74.
PUBMED | CROSSREF
4. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. *Am J Respir Crit Care Med* 2014;190(10):1102-10.
PUBMED | CROSSREF

5. Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Müller B. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. *Crit Care Med* 2004;32(8):1715-21.
PUBMED | CROSSREF

6. 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(8844):515-8.
PUBMED | CROSSREF

7. Jeon K, Suh JK, Jang EJ, Cho S, Ryu HG, Na S, et al. Procalcitonin-guided treatment on duration of antibiotic therapy and cost in septic patients (PRODA): a multi-center randomized controlled trial. *J Korean Med Sci* 2019;34(14):e110.
CROSSREF

8. Rhee C. Using procalcitonin to guide antibiotic therapy. *Open Forum Infect Dis* 2016;4(1):ofw249.
PUBMED | CROSSREF