Serum Procalcitonin Is a Candidate Biomarker to Differentiate Bacteremia from Disease Flares in Patients with Inflammatory Bowel Disease

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See "Usefulness of Measuring Serum Procalcitonin Levels in Patients with Inflammatory Bowel Disease" by Sook Hee Chung, et al. on page 574, Vol. 10. No. 4, 2016

In patients with inflammatory bowel disease (IBD), discriminating between bacterial infections and disease flares is often difficult due to the similar clinical presentations and laboratory findings. The differentiation in patients with IBD is important because treatments for each clinical condition are different and commonly opposite. Especially, early detection and treatment of infection in the disease state requiring immunosuppression have very significant impacts on good prognosis.

The white blood cell count, erythrocyte sedimentation rate, and C-reactive protein (CRP) level are not always helpful in distinguishing between the clinical conditions in IBD patients because these markers are elevated not only in infectious conditions, but also when the underlying disease flares.¹⁻³ Moreover, inflammatory signs can be masked and the CRP level decreased with corticosteroid therapy or immunosuppression, making CRP inconsistently reliable as a biomarker for bacterial infection in these clinical conditions.⁴

Recently, procalcitonin has been focused as a new biomarker to distinguish between bacterial infections and another inflammatory process. Procalcitonin is a precursor protein of calcitonin with a molecular weight of 13 kDa, produced by the C cells of the thyroid gland. During infection, procalcitonin is known to be synthesized and secreted from extrathyroidal area such as lung, liver, pancreas, and colon. Recently, the level has been measured routinely in some intensive care and surgery units to detect rapid evidence of bacteremia or to differentiate pancreatitis with infected necrosis from noncomplicated pancreatitis more easily.⁵

The reason why procalcitonin is worthy of more attention than other acute phase proteins is that the level is increased by

infection stimuli, not by abacterial inflammatory stimuli such as IBD flares. The more usefulness of procalcitonin to differentiate bacterial infections, compared to CRP, has also been proved in other study of various autoimmune diseases. The CRP level had no additive value when combined with the procalcitonin level to determine bacterial infections.⁶

Considering the mechanism of increasing serum procalcitonin, the role of bacterial endotoxin and mediators released in response to bacterial infections (that is, interleukin-1b [IL-1b], tumor necrosis factor α [TNF- α], and IL-6) is important.⁷ And procalcitonin strongly correlates with extent and severity of bacterial infections. During infections associated with marked TNF- α release, such as Gram-negative infections, the highest procalcitonin levels were seen. Meanwhile, procalcitonin levels do not increase in mycobacterial infections and viral illness.^{1,5} Because upregulation of procalcitonin is attenuated by interferon γ , a cytokine released in response to viral infections, procalcitonin is more specific for bacterial infections, not viral illnesses.¹

Fortunately, procalcitonin levels seem not to be affected by immunosuppressive agents in patients with bacterial infection. This would be a big advantage of procalcitonin to be recommended to detect bacterial infection for patients with inflammatory disease in immunosuppressive treatment.^{5,8}

Chung *et al.*⁹ compared the serum procalcitonin levels according to disease activity and the presence of infection, suggesting procalcitonin can be a useful marker for localized bacterial infection as well as sepsis. However, the usefulness of procalcitonin for detecting localized infection should be cautious. The data from this article showed that the median serum procalcitonin

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levels in the IBD and intestinal Bechet's disease (BD) with localized infection was higher than those without infection, however, the levels were still within normal range. Despite procalcitonin is stimulated variously depending on the nature of the causative infectious agent, the typical reference value of procalcitonin to distinguish bacterial infections from noninfectious inflammation is above 0.5 ng/mL (sensitivity 65% and specificity 96%). In one study, procalcitonin levels >1.2 ng/mL were always evidence of bacterial infection and the cue for starting antibiotic treatment. However, although the serum procalcitonin is less than 0.5 ng/mL, infection cannot be excluded completely; localized infection or very early stage of infection may be possible. Therefore serum procalcitonin levels often need to be correlated clinically and repeat after several hours to prevent missing serious infection.^{1,5} After a bacterial stimulus in healthy volunteers, the procalcitonin shows a very rapid response within 4 hours, reaching peak levels after 6 hours, and maintaining a plateau between 8 hours and 24 hours.^{2,6} The time point of measurement during clinical progress can influence the level of serum procalcitonin.

Considering the various or fluctuating levels of procalcitonin, it is suggested to examine the association between infection and serum procalcitonin level irrespective of disease activity using a categorical variable of the level above 0.5 ng/mL, not using a continuous variable in this article.

As the authors mentioned in discussion, the levels of serum procalcitonin in this article were significantly higher only in septic condition. The median level of serum procalcitonin in localized infection status was within normal range.⁹ Moreover, the levels were not significantly different between localized infection and noninfection status in the same activity diseases. From these findings, the measurement of serum procalcitonin seems to have limitations to detect combined infections in early stage in IBD patients. Therefore, it was still not concluded serum procalcitonin would be useful to differentiate all kinds of infection with noninfection status in IBD patients. Meanwhile, we believe there seem to be room for serum procalcitonin to detect severe infection or septic condition in IBD patients during immunosuppressive treatment. As mentioned above, CRP lacks specificity and sensitivity for bacterial infections, especially in immunosuppressive treatment. Although the very small number of patients with sepsis in this article made it difficult to concrete conclusion, the data showed the significantly higher level of serum procalcitonin at least in active intestinal BD with sepsis. Considering the occasional difficulty to differentiate severe combined infection from nonresponsive flared disease during treatment, especially for severe disease of IBD, this article is meaningful to demonstrate that serum procalcitonin is potential as a biomarker for assessing the combined infection in active

IBD or intestinal BD.

In conclusion, serum procalcitonin is more useful than CRP to differentiate infectious complications from disease flares in IBD patients. Considering it can be upregulated by bacterial endotoxin and the released mediators from infection, the issued state of infection would be severe clinical condition such as bacteremia or systemic inflammatory response syndrome including sepsis. In this regard, even if it did not be proven perfectly, the authors' suggestion that serum procalcitonin is useful to differentiate significant bacterial infections from IBD flares are thought to be reasonable and meaningful.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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