Letter to the Editor

Excluding Severe Bacterial Infection in Neutrophilic Dermatoses with Systemic Manifestations: Negative Predictive Value of Procalcitonin

Dear Editor,

Extensive neutrophilic activation and infiltration occur in a number of dermatological conditions, resulting in typical features of pyrexia, neutrophilia, and raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These conditions are namely generalised pustular psoriasis, acute generalised exanthematous pustulosis (AGEP) and Sweet syndrome, and they are termed as neutrophilic dermatoses with systemic manifestations. Their presentation is similar to that in patients with severe bacterial infections, such as severe pneumonia, peritonitis, meningitis, pyelonephritis and sepsis.

Early differentiation between neutrophilic dermatoses with systemic manifestations and severe bacterial infection is important due to the opposing treatment approaches. Whilst patients who have neutrophilic dermatoses with systemic manifestations require immunosuppressive therapy,[1,2] patients with severe bacterial infections require antibiotic therapy, and the use of immunosuppressive therapy should be avoided.

In the last decade, extensive research has been undertaken to study the diagnostic value of procalcitonin in bacterial infections.[3-6] The primary objective of this study is to evaluate the predictive value of procalcitonin for the presence of severe bacterial infections in patients who have neutrophilic dermatoses with systemic manifestations. If the procalcitonin levels in these patients are not elevated, clinicians can better decide if they can be commenced promptly on immunosuppressant for their underlying skin condition. The secondary objective is to evaluate if procalcitonin levels differ between generalised pustular psoriasis and AGEP, as it is clinically and histologically difficult to distinguish these 2 conditions.

Materials and Methods

Inpatients with a clinical diagnosis of generalised pustular psoriasis, AGEP or Sweet syndrome who were referred to the dermatology service in a tertiary hospital in Singapore, and who had their data recorded between May 2012 and April 2015, were evaluated retrospectively. Their diagnoses were made clinically and some patients had histopathological correlation. Severe bacterial infection was defined as either severe pneumonia resulting in shock or requiring mechanical ventilation, peritonitis, meningitis or bacteraemia. Bacteraemia was determined by a positive blood culture; cultures growing only coagulase-negative *staphylococci*—a typical contaminant during blood culture collection—were excluded. Patients with lower urinary tract infections or skin infections such as cellulitis were not classified as having a severe bacterial infection as physicians or dermatologists do not usually hesitate to commence immunosuppressant concurrently with antibiotic treatment in this group of patients and they do not usually constitute the clinical conundrum dermatologists face. Patients who did not have their procalcitonin levels measured during their hospitalisation were excluded from the study. Serum procalcitonin were measured using Roche Diagnostics' Roche Cobas e601, which utilises electrochemiluminescent immunoassay technology with a lower detection limit of 0.03 ug/L and a functional sensitivity of <0.06 ug/L. A procalcitonin level of >0.5 ug/L was considered as elevated[7] in keeping with previous investigations on the use of procalcitonin in sepsis.[3,7]

Our study was a retrospective review and most patients were referred to the dermatology department. As such, there were no stipulated guidelines for the physicians-in-charge on when to measure the patients' procalcitonin level and the frequency of its measurement. Procalcitonin was frequently measured based on the clinicians' individual practice and it was observed to be measured at different intervals over the course of the patients' hospitalisation, subjected to the primary physicians' choice. We then analysed the data based on the highest procalcitonin level measured during the patients' hospitalisation.

Mann-Whitney U test was used to evaluate the statistical difference between procalcitonin levels in the various diseases. Receiver operating characteristic (ROC) analysis was done to evaluate serum procalcitonin while CRP test was used to diagnose severe bacterial infections among patients with neutrophilic dermatoses. The ROC curve illustrates the diagnostic ability of whether the patient has severe bacterial infections.

In conjunction with the ROC analysis, Youden index was used to determine the threshold value for which procalcitonin optimally differentiates patients with and without a concurrent severe bacterial infection. The maximum value

of the index was used to select the optimum cutoff point of the procalcitonin test, which was 1.3 ug/L. The study was approved by the institution's ethics review board.

Results

There were a total of 59 patients (26 males and 33 females) who were diagnosed with neutrophilic dermatoses with systemic manifestations but only 41 patients had their procalcitonin measured during hospitalisation. The mean age of our patients was 60.0 + 20.9 years and none of them were pregnant.

Thirty-six had generalised pustular psoriasis, 16 had AGEP and 7 had Sweet syndrome. There were 7 patients with severe bacterial infections—4 had bacteraemia, 2 had severe pneumonia and 1 had multiple intra-abdominal collections. Of the 7 patients who had severe bacterial infections, all of them had a procalcitonin value of >0.5 ug/L (mean, 16.40; range, 1.33 to 47.09) (Fig. 1). Four of these 7 patients died, 3 of whom had a procalcitonin level of >7 ug/L.

Thirty-four patients who had neutrophilic dermatoses with systemic manifestations did not have severe bacterial infections (Fig. 2). A procalcitonin cutoff level of >0.5 ug/L has 100% sensitivity and 67.6% specificity in predicting concurrent severe bacterial infections in patients who have neutrophilic dermatoses with systemic manifestations (Table 1).

ROC analysis of serum procalcitonin levels demonstrated a good value at 0.912 (P = 0.001; 95% CI, 0.822 to 0.100) (Fig. 3). This indicated that in almost 91.2% of all possible pairs of subjects—in which one was the case (had a severe bacterial infection) and the other a control (did not have a severe bacterial infection)—serum procalcitonin would assign a higher probability to the former. In contrast, the ROC for serum CRP was fair with a value of 0.660. This meant that CRP, as a marker to differentiate severe bacterial infections among patients who have neutrophilic dermatoses with systemic manifestations, only performed 16.0% better than chance.
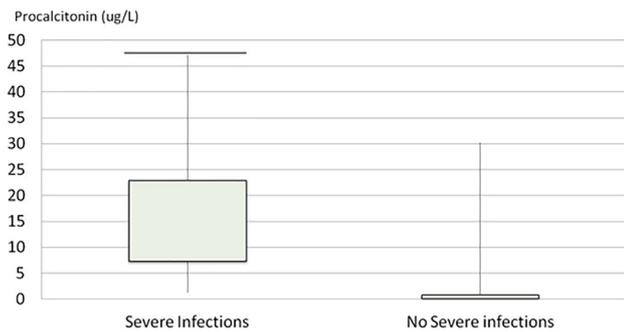

Fig. 1. This diagram shows the procalcitonin values in patients who have neutrophilic dermatoses with systemic manifestations according to the absence and presence of severe bacterial infection. The data is depicted as box-plot diagrams, with the box encompassing the range of values from the 25% percentile (lower bar) to the 75% percentile (upper bar). The horizontal line within the box represents the median and the vertical lines below the box signify the maximum and minimum values.
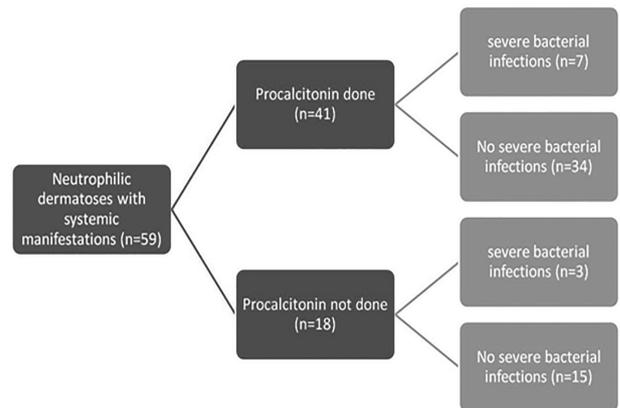

Fig. 2. Flowchart of patients with neutrophilic dermatoses with systemic manifestations.

Table 1. Sensitivity and Specificity of Using a Cutoff Value of 0.5 Ug/L and 1.3 Ug/L for Procalcitonin in Distinguishing Severe Bacterial Infections in Patients who Have Neutrophilic Dermatoses with Systemic Manifestation

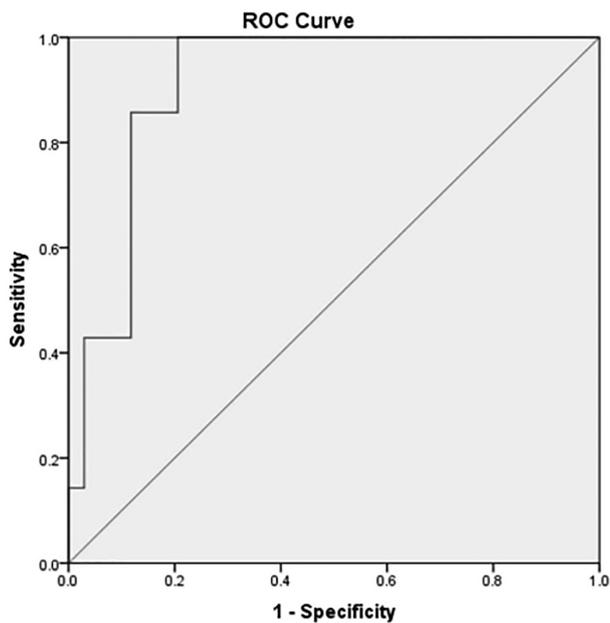| Disease	Patients with Significant Bacterial Infection (Procalcitonin >0.5 ug/L) (n = 41)		Patients with Significant Bacterial Infection (Procalcitonin >1.3 ug/L) (n = 41)	
	Yes	**No**	**Yes**	**No**
Raised procalcitonin				
Yes	7	11	7	7
No	0	23	0	27
Sensitivity	1.00		1.00	
Specificity	0.676		0.794	
Negative predictive value	1.00		1.00	
Positive predictive value	0.389		0.500	

Fig. 3. Prediction of severe bacterial infection ROC curve, with area under curve for procalcitonin = 0.912.

With a Youden index of 0.794, a serum procalcitonin cutoff level of 1.3 ug/L gives 100% sensitivity and 79.4% specificity in predicting concurrent severe bacterial infections in patients who have neutrophilic dermatoses with systemic manifestations. This suggests that a higher cutoff value of serum procalcitonin performed better in identifying severe bacterial infections among patients with neutrophilic dermatoses with systemic manifestations.

Using the Mann-Whitney U test, there was no significant difference between procalcitonin in patients with generalised pustular psoriasis and AGEP.

Discussion

Procalcitonin is a 116-amino acid precursor of calcitonin. In healthy subjects, the thyroid C cells are the only tissue which transcribe and translate the procalcitonin gene. Only a small amount of procalcitonin is released into the general circulation such that in healthy individuals, procalcitonin concentration is <0.05ug/L. In the presence of bacterial infection, however, procalcitonin production is activated in all parenchymal tissues and concentrations rapidly increase.[8] Procalcitonin production caused by these tissues is stimulated by 2 mechanisms—directly by bacterial endotoxins and lipopolysaccharides, and indirectly by inflammatory mediators, namely tumour necrosis factor-alpha (TNF-alpha), interleukin-6 and interleukin-1. During infections associated with marked TNF-alpha release, such as Gram-negative infections and malaria, marked

procalcitonin elevation is seen.[9] Because procalcitonin level is attenuated by interferon-gamma (a cytokine released in response to viral infections), procalcitonin is a more specific marker of bacterial infections. It is mainly degraded by proteolysis, and to a lesser extent, excretion through the kidneys.[10]

It is important to differentiate patients who have a flare of solely neutrophilic dermatoses with systemic manifestations from those who have concurrent severe bacterial infections. In sepsis, the traditional gold standard has been blood culture, but this method lacks sensitivity as causative microorganisms is detected only in 30% to 50% of patients with suspected bloodstream infection.[11]

It was previously found that a procalcitonin level of <0.5 ng/L had a high negative predictive value for the exclusion of sepsis while high levels (>2 ng/L) indicated severe sepsis or septic shock in patients admitted to the general medicine team or medical intensive care unit.[12] In our study, a procalcitonin cutoff of 1.3 ug/L conferred an excellent sensitivity and negative predictive value for concurrent severe bacterial infections in patients who had neutrophilic dermatoses with systemic manifestations. In all 27 patients who had a procalcitonin value of <1.3 ug/L, none of them were diagnosed with a severe bacterial infection. This, to our knowledge, is the first study investigating the utility of procalcitonin in predicting concurrent severe bacterial infections in patients who had neutrophilic dermatoses with systemic manifestations.

The results of our study indicated that procalcitonin could be useful in ruling out a concurrent severe bacterial infection in patients who had neutrophilic dermatoses with systemic manifestations. Out of 23 patients with non-elevated procalcitonin level, 22 received systemic antibiotics. In such cases, the focus and approach of management would be on reducing uncontrolled activation of the innate immunity rather than to treat infection, in which more aggressive anti-inflammatory agents can be confidently used rather than stronger antibiotics. In addition, procalcitonin is a relatively quicker and minimally invasive test compared to other tests such as blood culture and radiography that can be used as a tool for ruling out infections. Procalcitonin results could be confirmed in less than a day and a negative result could mean that immunosuppressive therapy would be started much faster rather than having to wait for more traditional tests such as blood cultures to be reported.

In our data, out of 7 patients who were diagnosed with Sweet syndrome, only 5 had their serum procalcitonin levels measured. In these 5 patients, only 1 patient had concomitant myelodysplastic syndrome and myelofibrosis. None of the patients with Sweet syndrome in our study had associated ulcerative colitis, Crohn's disease, rheumatoid arthritis or lupus erythematosus. In our literature review,

serum procalcitonin has been found in previous studies to be a promising marker in haematological malignancy, inflammatory bowel disease and autoimmune diseases to aid in the differentiation between bacterial infections and inflammatory flares.[13-16] In these studies, serum procalcitonin was measured using instruments from different manufacturers with different lower detection limits. Thus, comparison of quantitative serum procalcitonin levels between studies may be difficult. Serum procalcitonin levels are not significantly different between pregnant women and healthy controls.[17]

There are several limitations of our study. Firstly, our study sample size was small, which would limit the generalisability of the ROC analysis to the general population. Secondly, the number of patients who had a concurrent diagnosis of severe bacterial infection was markedly lesser than the number of patients who did not have a severe bacterial infection. Thirdly, in our study, we only included patients with generalised pustular psoriasis, AGEP and Sweet syndrome as they shared a similarity of systemic neutrophilic activation with the main manifestation in the skin. However, these 3 conditions have different pathogenetic mechanisms of neutrophilic activation and are not a uniform entity. We believe larger future prospective studies will be useful to validate our findings and study the outcomes of early implementation of immunosuppressive therapy guided by procalcitonin levels or trends.[18]

Conclusion

The study results indicate that in patients with neutrophilic dermatoses with systemic manifestations with a procalcitonin value of <1.3 ug/L, it is very unlikely that their clinical manifestations of systemic inflammation are due to a severe bacterial infection. In such instances, immunosuppressant therapies, which are typically withheld for fear of causing fulminant sepsis, can be reasonably instituted early to treat their diseases.

REFERENCES

1. Robinson A, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF Jr, et al. Treatment of pustular psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2012;67:279-88.

2. Villarreal-Villarreal CD, Ocampo-Candiani J, Villarreal-Martínez A. Sweet Syndrome: A Review and Update. Actas Dermosifiliogr 2016;107:369-78.

3. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med 2011;9:107.

4. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med;164:396-402.

5. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13:426-35.

6. Tamaki K, Kogata Y, Sugiyama D, Nakazawa T, Hatachi S, Kageyama G, et al. Diagnostic accuracy of serum procalcitonin concentrations for detecting systemic bacterial infection in patients with systemic autoimmune diseases. J Rheumatol 2008;35:114-9.

7. Pugin J, Meisner M, Leon A, Gendrel D, Lopez AF. Guide for the clinical use of procalcitonin (PCT). Available at: http://tools.thermofisher.com/content/sfs/brochures/PCT-Guide.pdf. Accessed on 16 May 2016.

8. Snider RH Jr, Nylen ES, Becker KL. Procalcitonin and its component peptides in systemic inflammation: immunochemical characterisation. J Investig Med 1997;45:552-60.

9. Delèvaux I, André M, Colombier M, Albuisson E, Meylheuc F, Bègue RJ, et al. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? Ann Rheum Dis 2003;62:337-40.

10. Davies J. Procalcitonin. J Clin Pathol 2015;68:675-9.

11. Murray PR, Masur H. Current approaches to the diagnosis of bacterial and fungal bloodstream infections in the intensive care unit. Crit Care Med 2012;40:3277-82.

12. Rimac V. Procalcitonin – Potential, limitations and availability. Signa Vitae 2015;10:84-6.

13. Meidani M, Khorvash F, Abolghasemi H, Jamali B. Procalcitonin and quantitative C-reactive protein role in the early diagnosis of sepsis in patients with febrile neutropenia. South Asian J Cancer 2013;2:216-9.

14. Chung SH, Lee HW, Kim SW, Park SJ, Hong SP, Kim TI, et al. Usefulness of measuring serum procalcitonin levels in patients with inflammatory bowel disease. Gut Liver 2016;10:574-80.

15. Tamaki K, Kogata Y, Sugiyama D, Nakazawa T, Hatachi S, Kageyama G, et al. Diagnostic accuracy of serum procalcitonin concentrations for detecting systemic bacterial infection in patients with systemic autoimmune diseases. J Rheumatol 2008;35:114-9.

16. Shomali W, Hachem R, Chaftari AM, Jiang Y, Bahu R, Jabbour J, et al. Can procalcitonin distinguish infectious fever from tumor-related fever in non-neutropenic cancer patients? Cancer 2012;118:5823-9.

17. Bilir F, Akdemir N, Ozden S, Cevrioglu AS, Bilir C. Increased serum procalcitonin levels in pregnant patients with asymptomatic bacteriuria. Ann Clin Microbiol Antimicrob 2013;12:25.

18. 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 multicenter randomized controlled trial. Lancet 2010;375:463-74.

Pei Ming <u>Yeo</u>, [1]*MBBS*, Yik Weng <u>Yew</u>, [2]*MBBS, MPH (Harvard)*,
Hong Liang <u>Tey</u>, [2,3]*MBBS, FRCP (Edin), FAMS (Dermatology)*

[1]Department of General Medicine, Tan Tock Seng Hospital, Singapore
[2]Department of Dermatology, National Skin Centre, Singapore
[3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Address for Correspondence: Dr Tey Hong Liang, Department of Dermatology, National Skin Centre, Singapore, 1 Mandalay Road, Singapore 308205.
Email: teyhongliang111@yahoo.com