Differences of serum procalcitonin levels between bacterial infection and flare in systemic lupus erythematosus patients

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Abstract. Differentiate bacterial infections from flare in SLE patients is difficult to do because clinical symptoms of infection is similar to flare. SLE patients with infection require antibiotic therapy while in flare diseases require increased immunosuppressant. Procalcitoning (PCT), a biological marker, increased in serum patients with bacterial infections and expected to be a solution of problem. The aim of this study was to examine the function of PCT serum as marker to differentiate bacterial infection and flare in SLE patients. This cross-sectional study was conducted in Adam Malik Hospital from January-July 2017. We examined 80 patients SLE flare (MEX-SLEDAI>5), screen PCT and culture according to focal infection. Data were statistically analyzed. 80 SLE patients divided into 2 groups: bacterial infection group (31 patients) and non-infection/flare group (49 patients). Median PCT levels of bacterial infection group was 1.66 (0.04-8.45)ng/ml while flare group was 0.12 (0.02-0.81)ng/ml. There was significant difference of serum Procalcitonin level between bacterial infection and flare group in SLE patients (p=0.001). Procalcitonin serum levels can be used as a biomarker to differentiate bacterial infections and flare in SLE patients.

1. Introduction
Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease characterized by widespread inflammation, affecting every organ or system in the body and more commonly found in women especially at the age of 15-40 years.[1]

The main causes of death in SLE patients are major organ failure caused by active disease (flare), infections, and cardiovascular disease. Late diagnosis, poor adherence to therapy, and persistent SLE disease activity are important predictors of the prognosis of SLE patients.[2] SLE patients have a high risk of infection caused by impaired intrinsic immune responses, immunosuppressant drug use, and vital organ complications from the SLE disease.[3,4] Prognosis of SLE patients has an increase in mortality by 3-5 times compared to general population.[2]

Differentiate bacterial infections from flare in SLE patients is a challenge for rheumatology clinicians.[5] This is very fundamental and quite difficult to do because the clinical symptoms of the infection is similar to flare disease (active lupus), making it difficult to determine the presence or absence of infection.[6,7] In SLE patients with infection require antibiotic therapy with decreased doses or amounts of immunosuppressant while in flare require increased immunosuppressant. The
treatment of bacterial infections and flare is so opposite that making the right diagnosis decisions becomes crucial in establishing further therapy strategies.[7]

Procalcitonin (PCT), a precursor of calcitonin peptide produced from parenchymal cells, is a biological marker that increased in serum patients with bacterial infection.[8] This marker has been shown to be more specific than CRP and leukocytes for inflammatory processes caused by bacterial and fungal infections and may be helpful in detecting acute infection or non-infection.[9] In autoimmune disease, serum PCT levels have been reported no increase to slightly increase, so PCT can be a good candidate to differentiate infections from flare in SLE patients.[10,11] Previous studies have shown PCT can be used as a marker for bacterial infection in SLE but there are still controversial results in other studies.

2. Methods

2.1. Patient Selection
This study was a cross-sectional study design on eighty consecutive SLE flare patients that were admitted to General Hospital Haji Adam Malik Medan in January-July 2017. Diagnosis of SLE was made according to American College of Rheumatology (ACR) 1997 revised criteria.[12] Inclusion criteria was SLE flare (MEX-SLEDAI>5) and exclusion criteria were patients with severe renal insufficiency (GFR <30ml/min), fungal infections, massive stress (severe trauma, burns, surgery, cardiac shock), malaria, severe liver cirrhosis (Child Pugh C), thyroid cancer and small cell lung cancer. Procalcitonin serum, MEX-SLEDAI score, Anti-dsDNA, ANA test, culture according focal infection and details of infection and other clinical characteristics were recorded. This study was approved by local ethics committee.

2.2. MEX-SLEDAI score
Disease activity SLE was assessed using MEX-SLEDAI scores. MEX-SLEDAI score has a score range of 0 to 32, where the higher the score indicates the more severe the activity of SLE disease. Lupus Flare or active lupus is defined as the MEX-SLEDAI score >5. Score <2 represents remission or inactive lupus and a score of 2-5 indicates the possibility of flare [13].

2.3. Definition of bacterial infection
Diagnosis of bacterial infection based on the results of positive culture examination of pathogenic microorganisms. In this study, we examined culture according focal infection (blood, urine, sputum, pus) in each study subjects. Positive fungal infections will be excluded in this study.

2.4. Measurement of PCT
Serum Procalcitonin (PCT) examination was performed by using immunoluminometric assay with technical specification VIDAS B.R.A.H.M.S. PCT (BioMerieux). This examination has PCT coverage of 0.05-200 ng/ ml.

2.5. Statistical Methods
Data analysis was performed through univariate and bivariate analyses using the SPSS 22nd version (SPSS Inc., Chicago) with a 95% confidence interval. Bivariate analysis was performed using Mann-Whitney U test with significance p<0.05.

3. Result
This study was followed by 80 patients who met the inclusion criteria, divided into 2 groups of bacterial infections (n=31) and non-infection/ flare (n=49). Median MEX-SLEDAI score in the bacterial infection group was 9 whereas in the non-infection/ flare group was 8. The median of Anti-dsDNA in the infection group was 355 (31.4-1378) while in the non-infection/ flare group was 381 (47-1451). The median of ANA test in the infection group was 107.7 (2.4-260) while in the non-
infection/flare group was 88 (3.9-303). The median of serum Procalcitonin level in the infection group was 1.66 (0.04-8.45) while in the non-infection/flare group was 0.12 (0.02-0.81). (Table 1)

**Table 1. Basic characteristics of SLE patients.**

| Characteristics       | Bacterial Infection Group (n=31) | Non-Infection / Flare Group (n=49) | p-value |
|-----------------------|----------------------------------|-----------------------------------|---------|
| Sex                   |                                  |                                   |         |
| Men                   | 5 (16.1)                         | 4 (8.2)                           | 0.298   |
| Women                 | 26 (83.9)                        | 45 (91.8)                         |         |
| Age                   | 26.32 ±6.32                      | 27.27 ±7.87                       | 0.789   |
| Occupation            |                                  |                                   |         |
| Student               | 7 (22.6)                         | 13 (26.5)                         |         |
| Housewife             | 13 (41.9)                        | 21 (42.9)                         |         |
| Entrepreneur          | 5 (16.1)                         | 7 (14.3)                          |         |
| Farmer                | 5 (16.1)                         | 4 (8.2)                           |         |
| Others                | 1 (3.2)                          | 4 (8.2)                           |         |
| MEX-SLEDAI            | 9 (6-17)                         | 8 (6-20)                          | 0.072   |
| Anti dsDNA            | 355 (31.4-1378)                  | 381 (47-1451)                     | 0.984   |
| ANA Test              | 107.7 (2.4-260)                  | 88 (3.9-303)                      | 0.992   |
| Procalcitonin (PCT)   | 1.66 (0.04-8.45)                 | 0.12 (0.02-0.81)                  | 0.001   |

*a* categorical data : n (%)  
*b* numeric data, mean ± SD  
*c* numeric data, median (min-max)

In this study, a Mann-Whitney U test showed that there were no significant differences in demographic data, MEX-SLEDAI score, Anti ds-DNA and ANA Test between bacterial infection group and non-infection/flare group in SLE patients but there was significant difference of serum Procalcitonin level between bacterial infection group and flare group in SLE patients (p=0.001).

The bacterial infection group included 32 pathogens microorganisms from 31 cases of bacterial infection with most pathogens were *Escherichia coli* (21.8%), *Klebsiella pneumonia* (21.8%), *Acinetobacter baumannii* (12.5%), *Pseudomonas aeruginosa* (12.5%), and *Staphylococcus aureus*.
The infection site came from lung (75%) and urinary tract (25%). The mean of PCT serum in the bacterial infection group was $2.61 \pm 2.5$ ng/ml. Detailed pathogens microorganisms were listed in Table 2.

### Table 2. Pathogens microorganisms in SLE patients.

| Pathogens                      | n (%) |
|--------------------------------|-------|
| Acinetobacter baumanii         | 12.5  |
| Aeromonas hydrophilia          | 3.2   |
| Enterobacter aerogenes         | 3.2   |
| Enterobacter cloacae           | 6.2   |
| Escherichia coli               | 21.8  |
| Klebsiella pneumonia           | 21.8  |
| Pseudomonas aeruginosa         | 12.5  |
| Staphylococcus aureus          | 9.4   |
| Stenotrophomonas maltophilia   | 3.2   |
| Stephanoascus ciferri           | 6.2   |

### 4. Discussion

Procalcitonin (PCT) is a precursor of calcitonin hormone polypeptide which was first recognized as C parafollicular cells from the thyroid gland. PCT is a good indicator of detecting systemic inflammatory bacterial infections with normal concentration are $<0.05$ ng/ml, but in systemic inflammatory conditions, especially bacterial infections, PCT was produced in large quantities by many body tissues.[14] Elevated Procalcitonin level influenced by bacterial endotoxin and other inflammatory mediators such as IL-1β. PCT can be detected within 2 hours after the onset of infection and may return to normal once the infection has disappeared, so it can be applied for evaluation of the progression of bacterial infection and efficiency of antibiotic therapy.[7,8]

Serum PCT levels higher in bacterial infection group than in non-infection/flare group with median value of $1.66 (0.04-8.45)$ ng/ml and 0.12 (0.02-0.81) ng/ml. There was a significant difference of serum procalcitonin levels between bacterial infection group and non-infection/flare groups in SLE patients (p=0.001). These results were consistent with study conducted by Shin et al that procalcitonin levels in the bacterial or fungi infection group (12 patients) were higher than in flare group (7 patients) with PCT value of $0.98 \pm 0.12$ ng/ml and $0.24 \pm 0.18$ ng/ml (p<0.01).[15] Similar results were also found in the Ho et al study that Procalcitonin levels were higher in the bacterial infection group (19 patients) were $7.11 (1.38-42.8)$ ng/ml while in the flare group (30 patients) were $0.06 (0.05-0.20)$ ng/ml with p value $<0.001$.[16] The study of Bador et al stated that Procalcitonin levels were higher in the bacterial infection group (10 patients) was $0.19 (0.02-2.51)$ ng/ml while in the flare group (24 patients) was $0.08 (0.04-0.47)$ ng/ml with p value 0.003.[17]

However, the results of study by Lanoix et al was contrary to the others. The results of PCT levels in the bacterial infection group (5 patients) were $0.06 (0.05-0.09)$ ng/ml while in the flare group (16 patients) were $0.063 (0.029-0.68)$ ng/ml with p value 0.80. This study has limitations in sample size, only 5 patients in bacterial infections group, so the possibility of bias can occurs due to very small sample size.[7,18]

Bacterial infections are a major cause of infection in SLE with the most frequent sites of infection are respiratory tract, urinary tract, and skin. The risk factor predispose of infection in SLE are active disease, lymphopenia, immunosuppressive therapy, renal disorder and central nervous system disorder.[19] In this study, *Escherichia coli* and *Klebsiella pneumonia* were the most common pathogen microorganisms in SLE (21.8%). These results were consistent with study conducted by Bosch et al that *Escherichia coli* was the most commonly microorganism (21.3%). Other prospective study in the Hopkins Lupus Cohort concluded that SLE activity was a predictor factor for hospitalization because of infection. In Asian, Gram negative bacilli are the most common microorganism responsible for bacteremia and Gram positive coccid are more often encountered in
Western. *Staphylococcus aureus* was the leading cause of Gram positive bacteremia and *Escherichia coli* as the cause of Gram negative bacteremia. [20]

The limitation of this study was the sample size was small, further research is required with larger samples. In addition, the possibility of bias may occur when the collection and interpretation of culture such as positive bacterial culture sometimes can be interpreted as a result of colonization and negative results are unlikely to ensure the absence of infection.

5. Conclusion

Procalcitonin serum levels can be used as a biomarker to differentiate bacterial infections and flare in SLE patients.

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