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RELATIONSHIP BETWEEN PROCALCITONIN LEVEL AND BACTERIAL TYPE IN UROSEPSIS PATIENTS AT THE H. ADAM MALIK CENTRAL GENERAL HOSPITAL IN MEDAN

Mudatsir Resident of Surgery Departement Sumatera Utara University

Ramlan Nasution* Lecturer of Surgery Departement Sumatera Utara University *Corresponding Author

Syah Mirsya Warli Lecturer of Surgery Departement Sumatera Utara University

ABSTRACT

Urosepsis is defined as sepsis (septicemia syndrome) which is caused by an infection of the urinary tract. In sepsis, increased levels of procalcitonin in the blood have a significant value that can be used as biomarkers of sepsis. This study aims to correlate the levels of procalcitonin with the type of bacteria in urosepsis patients. This study is a retrospective cross-sectional study, where the samples assessed were inpatients with a diagnosis of urosepsis at H. Adam Malik General Hospital Medan from December 1, 2015 to July 31, 2018. Data were collected from medical records. Of the 58 study samples, 30 samples (51.7%) were male and 28 others (48.3%) were women. The age of the patient has a mean of 51 years. Of the 17 samples with procalcitonin levels above 10, 15 of them had gram negative culture results. Based on the results of the analysis of the data obtained from this study, there was a significant relationship between the levels of procalcitonin and the type of gram bacteria.

INTRODUCTION

Urosepsis is defined as sepsis (septicemia syndrome) which is caused by an infection of the urinary tract. Infection in the urinary tract was diagnosed through examination of urine analysis and confirmed by the results of urine culture. Normally the urinary tract is free of bacteria. (Schaeffer et al, 2016). Urosepsis is part of a sepsis whose severity depends on the host's response. Sepsis is related to an excessive immune response that the body has to an infection (Sugimoto et al, 2013; Tongdagdu et al, 2016).

The reported death rates of severe sepsis and septic shock are 28-41% (Martin et al, 2000) where the source of infection is significantly from the urinary tract with cases of severe sepsis 9% and septic shock 31% (Levy et al, 2012). As with other sepsis syndromes, urosepsis develops from urinary tract infections which have high mortality and morbidity.

Urosepsis mortality reaches 20-49% when accompanied by shock (Harrison et al, 2006). According to surviving sepsis, sepsis deaths in hospitals were 39.8%, in the ICU it was 31.1%. (Martin et al, 2003). Patients who are more susceptible to urosepsis are elderly patients, diabetics, immunosuppressive patients (kidney transplant recipients), cancer chemotherapy patients, and AIDS (Angus, et al 2001).

The primary infectious microorganisms in the urinary tract are gram negative coliform bacteria such as Escherichia coli (50%), Proteus spp (15%), Klebsiella (15%), Enterobacter (15%), Pseudomonas aeruginosa (5%), and gram Bacteria positive, but the frequency is smaller which is around 15%. Clinical symptoms in urosepsis patients include: fever, chills, tachypnea, tachycardia, bacteria in the urine and blood (bacteremia) (Harrison et al, 2006). Procalcitonin is a calcitonin prohormone found in the human body. In sepsis, increased levels of procalcitonin in the blood have a significant value that can be used as a biomarker of sepsis (Soreng et al, 2011). Procalcitonin levels are categorized into values below 0.5 ng / mL (local bacterial infection), 0.5-2 ng / mL (sepsis), 2-10 ng / mL (severe sepsis), and values above 10 ng / mL (septic Shock). When compared with other sepsis biomarkers (eg CRP), procalcitonin is more sensitive and its levels are the fastest to rise after exposure to infection. In other studies, the rate of invasion of microorganisms in sepsis provided a rhythmic correlation with increases in blood procalcitonin levels (Jose et al, 2008).

Provision of appropriate antibiotic therapy will reduce procalcitonin levels in sepsis (Christ-Crain et al, 2008). In a previous study by Sugimoto koichi, et al., Conducted in the Department of Urology at West Osaka Hospital, Osaka, Japan in 2013 out of 37 patients procalcitonin levels between 2-10 ng / mL obtained 100% positive culture results, and levels greater than 10 ng / mL obtained 88.9% positive culture results. Gram negative bacteria are believed to be the most common cause of urosepsis cases, around 85%, while 15% of other cases of urosepsis are caused by gram positive bacteria (Sugimoto et al, 2013). Therefore, in this study researchers will relate the levels of procalcitonin with the type of bacteria in urosepsis patients at the H. Adam Malik Central General Hospital in Medan.

METHODS

This study is a retrospective analytic study with a cross sectional design. This research was carried out in the Urology Division of the Surgical Science Department of the Adam Malik Hospital in Medan. The time of the study was carried out from December 1, 2015 to July 31, 2018. The sample in this study was inpatients with a diagnosis of urosepsis at H. Adam Malik General Hospital, Medan. Based on the sample calculation formula, the minimum number of samples used for this study was 41 people.

Data is collected from medical records. All data that has been collected, recorded and grouped is then processed using a statistical processing program and analyzed univariately according to the research objectives

RESULTS

Of the 58 study samples, 30 samples (51.7%) were male and 28 others (48.3%) were women. The age of the patient has a mean of 51 years, with a standard deviation of 10.9. In all samples there was an increase in leukocyte levels, with an average blood leukocyte value of 22,500 / mm3. The value of procalcitonin levels in the sample was classified into 4 categories based on their value and severity. 17 patients (29.3%) had procalcitonin levels> 10 ng / mL classified as severe sepsis leading to shock, 15 people (25.9%) had procalcitonin levels between 2 to 10 ng / mL classified as sepsis and systemic infections, 12 people (20.7%) had procalcitonin levels of 0.5 to 2 ng/mL and were classified as systemic infections and 14 people (24.1%) had procalcitonin levels below 0.5 ng/mL which were classified as mild infections.

Table 1. Sample Characteristics

Variable	
Gender	
Male	30 (51.7%)
Female	28 (48.3%)
Age	51 ± 10.9
Leukocyte/mm^3	22.0 ± 12.7
Procalcitonin	
<0.5 ng/mL	14 (24.1%)
0.5 – < 2 ng/mL	12 (20.7%)
2 – <10 ng/ mL	15 (25.9%)
10 ng/ mL	17 (29.3%)

Table 2. Urine Culture

Species	Gram	n
Escherichia coli	Negatif	19
Enterococcus faecalis	Positif	9
Staphylococcus saprophyticus	Positif	7
Pseudomonas aeruginosa	Negatif	5
Bukholderia cepacia	Negatif	1
Staphylococcus aureus	Positif	4
Acinetobacter Baumannii	Negatif	4
Klebsiella pneumoniae	Negatif	5
Staphylococcus epidermidis	Positif	1
Proteus mirabilis	Negatif	1
Staphylococcus hominis	Negatif	1
Staphylococcus schiar	Positif	1

Table 3. Procalcitonin correlation with Gram type

Kadar PCT	Gram Negatif	Gram Positif	p-value
<0.5 ng/mL	5 (35.7%)	9 (64.3%)	0.019
0.5 – <2 ng/mL	6 (50.0%)	6 (50.0%)	
2 – <10 ng/mL	10 (66.7%)	5 (33.3%)	
10 ng/mL	15 (88.2%)	2 (11.8%)	

Of the 17 samples with procalcitonin levels above 10, 15 of them had gram negative culture results, while the other 2 had gram positive culture results. A total of 14 samples of procalcitonin levels were below 0.5 ng / mL, 5 of them had gram negative culture results and 9 samples had gram positive culture results.

Statistic analysis were performed to determine the relationship between PCT levels and culture results, and found a significant relationship between the two variables (p = 0.019)

DISCUSSION

Urosepsis is one of the most common urinary tract disorders. Many factors can affect the incidence of urosepsis, including obstruction, congenital abnormalities, stones, prostate enlargement, trauma, instrumentation, and other comorbidities (Leli C et al, 2015; Saikant R, 2017; Sugimoto, 2013). Prolonged urinary tract infections are the most frequent precursors of urosepsis, so culture is the right examination for patients to determine the pathogen causing urosepsis. (Sugimoto, 2013).

Gram negative bacteria are believed to be the most common cause of urosepsis, around 85%, while 15% of other cases of urosepsis are caused by gram-positive bacteria. Gram negative pathogens include *Escherichia coli* (50%), *Enterobacter* and *Klebsiella* (15%) and *Pseudomonas aeruginosa* (5%) (Kalra , 2009; Zhydkov, 2015). This is in line with the results of this study where the results of the culture found that the most common causes of urosepsis were gram negative bacteria with pathogens *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter Baumannii*, and *Klebsiella pneumoniae*.

Gram-positive and gram-negative bacteria activate different pathways, and result in the production of different proinflammatory cytokines in procalcitonin stimulation. Gram negative bacteria produce endotoxins that are produced from cell death resulting in higher procalcitonin values (Brodska H et al, 2013). A study comparing the increase in procalcitonin values between gram-positive and negative bacteria showed prospectively, with a procalcitonin cut-off value of 10.8 ng / mL, procalcitonin can be used as a reference in distinguishing the causes of infection between gram-positive and gram-negative bacteria with a sensitivity of 60% and specificity 82% (Limper M et al, 2010).

Another study with a cutoff point for procalcitonin levels of 15 ng / mL showing differences in procalcitonin levels could distinguish bacterial causes of infection with a specificity of 87.8%. Studies show differences in procalcitonin levels that are influenced by the type of bacteria that causes infection and the location of infection. Higher levels of procalcitonin were found in Enterobacteriaceae species compared to non-fermentative gram negative bacteria (Yan ST et al, 2016).

In patients with suspected sepsis, procalcitonin can be used to diagnose sepsis quickly and assess its severity (Schuetz P, 2013). This is needed because this condition is an emergency condition and the delay in treatment can be fatal. Procalcitonin can diagnose urosepsis with a sensitivity of 77%, and a specificity of 79%. Patients with serum proccalcitonin levels above 10 ng / dL are classified as severe sepsis (Jung B et al, 2013; Brodska H et al, 2013).

In this study, 17 samples showed severe sepsis with procalcitonin levels above 10 ng / mL with 15 of them with positive culture results for gram negative bacteria and 2 with gram-positive culture results. Meanwhile, there was a significant relationship between procalcitonin levels and the results of bacterial gram-positive and negative cultures.

The difference in procalcitonin levels in gram-positive and negative bacteria is still unclear, but several hypotheses indicate that there are differences in procalcitonin responses to gram-positive and negative bacteria involving lipoteichoic acid, bacterial molecular patterns, and expression of receptors in cells in the body. Gram-positive bacteria can activate the TLR2 pathway, while gram-negative bacteria activate the TLR4 pathway, causing differences in the different inflammatory responses of the body (Liu HH et al, 2017). Gram-negative bacillus secretes endotoxin which blocks the layer of liposaccharide which affects the activity of macrophages and neutrophils, and stimulates the production of IL-1, IL-6, TNF-alpha, and TNF-alpha. These cytokines will cause procalcitonin production from neuroendocrine cells, and increase serum procalcitonin levels. This causes a difference in the level of procalcitonin as a response to pathogens, both grampositive and negative. (Liu HH et al, 2017; Bilgili et al, 2018; Kalra O, 2009).

In a retrospective study, serum procalcitonin levels tended to be higher in gram negative bacteria than gram positive, with AUC 0.79. Other studies have shown an association where increased levels of procalcitonin can be used to predict the incidence of bacteremia caused by gram-negative bacteria. Another retrospective study shows that procalcitonin levels of 15 ng / mL can differentiate the occurrence of sepsis caused by gram negative bacteria compared to gram positive bacteria (He C et al, 2017). However, several studies also showed no association between procalcitonin levels from gram-positive and negative bacteria. These differences can be caused by differences in the number of study samples, differences in culture and distribution of bacteria as well as levels of procalcitonin (Bilgili et al, 2018).

Increased levels of procalcitonin tend to be higher in patients with gram-negative bacterial infections compared with gram-positive. Procalcitonin can be used as a biomarker that is useful in distinguishing pathogens that cause infection. Measuring procalcitonin levels in serum can be an important component in providing empirical therapy in patients with urosepsis (Brodska H et al, 2013; Yan ST et al, 2016; Limper M et al, 2010).

CONCLUSION

Based on the results of data analysis obtained from this study, there was a significant relationship between the levels of procalcitonin and the type of gram bacteria in urosepsis patients at H. Adam Malik Hospital Medan.

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