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CORRELATION BETWEEN TIME TO POSITIVITY BLOOD CULTURE AND PROCALCITONIN IN BACTEREMIA PATIENTS

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ABSTRACT

Bacteremia causes a high mortality rate. Early detection of bacteremia is very important. The gold standard for bacteremia is blood culture, which takes between 24-48 hours. Procalcitonin (PCT) is a marker of infection caused by bacteria that can be detected quickly in 2-6 hours. Time to Positivity (TTP) of blood culture is affected by the initial amount of bacteria and the addition of PCT stimulated by bacteria causing bacteremia where short TTP and high PCT show bad clinical conditions. This study aimed to investigate the correlation of TTP of blood cultures with PCT levels in bacteremia patients. The study design was cross-sectional, conducted on 46 bacteremia patients who met the inclusion and exclusion criteria, in patients with bacteremia. Time to positivity was calculated by Bactec 9050, and miniVIDAS B.R.A.H.M.S. analyzed level of PCT. Laboratory examinations were conducted in the Department of Clinical Pathology, Faculty of Medicine, North Sumatera University/Installation of Clinical Pathology of Adam Malik Hospital, Medan, during June – October 2016. There was a significant correlation between TTP blood culture and PCT in bacteremia patients ($p<0.05$) with r -0.294. There was no significant correlation between TTP and PCT in bacteremia, which was caused by Gram-positive bacteria or Gram-negative bacteria ($p>0.05$). Procalcitonin was significantly higher in bacteremia, which was caused by Gram-negative bacteria compared to Gram-positive bacteria ($p<0.05$). There was a significant correlation between TTP blood culture and PCT on bacteremia patients. Significantly higher levels of PCT in cases of bacteremia are more likely to be caused by Gram-negative bacteria than Gram-positive bacteria.

Key words: Time to positivity, blood culture, procalcitonin, bacteremia

INTRODUCTION

Bacteremia cases cause high morbidity and mortality. For immediate handling of the patient, the detection of bacteremia needs to be as short as possible. Although blood culture is the gold standard for detecting infections in the bloodstream, the results can only be obtained after 24 to 48 hours or more, which may lead to the delay of the patient's treatment.[1,2]

Time to Positivity (TTP) blood culture is the starting time of the sample incubated in the instrument until the alarm sign of germ growth. The bacterial load of blood culture is often assessed by the TTP and influenced by the concentration of pathogens in the primary sample and pathogenic species.[3] In addition to the initial inoculum, other factors affecting TTP are the volume of blood inserted into the culture bottle and the incubation conditions, collection time, processing parameters and delay of sample transfer.[3,4]

Some reports show that a short TTP is associated with poor clinical outcome and death, and may be used as an independent prognostic instrument in bacteremia caused by *Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli*, and as a surrogate marker for the output of bacteremia caused by *Streptococcus pneumonia*.[4-9]

Procalcitonin (PCT) is a prohormone of calcitonin synthesized by the thyroid gland cell, a functional protein consisting of 114-116 amino acids, which is found in high levels strongly associated with systemic bacterial infections and disease severity, first performed by Assicot *et al*. who differentiated bacterial meningitis and viral meningitis.[10,11] After adequate stimulus PCT can be detected in the circulation within 2-6 hours.[12] Procalcitonin levels correlate with the severity of the bacterial infection and bacterial count. High PCT levels have a strong positive predictive value of severe sepsis and septic shock.[11]

From the studies above in which a short TTP is associated with high morbidity and mortality and high PCT is associated with the severe clinical outcome on bacteremia. This study aimed to investigate the correlation of TTP of blood cultures

with PCT levels in bacteremia patients.

METHODS

This study was a cross-sectional study conducted in the Department of Clinical Pathology, Faculty of Medicine, Adam Malik Hospital from June to October 2016. The study population was patients with suspected bacteremia hospitalized in the Adam Malik Hospital, with inclusion criteria of two or more of the following: temperature <36ºC or >38ºC, leukocytes <4000/mm^3 or > 12.000/mm^3, tachypnea RR >24x/minute, HR tachycardia >90x/min, or hypotension. Patients with burns, thyroid carcinoma, polymicrobial growth, fungi, bacterial contaminants (coagulase negative Staphylococci with TTP >24 h, Bacillus spp. Diphtheroid) were excluded from this study. The sample of the research was the time when blood culture was performed, and growth of monomicrobial bacteria was shown.

Aseptic sampling was performed using CHG 0.5% swab alcohol (70% isopropyl alcohol, 0.5% chlorhexidine gluconate) for blood culture. Blood cultures were performed by inoculating/incubating 10 mL of blood into a BD Bactec Aerobic Plus bottle and incubated in the BACTEC 9050 immediately after sampling. The BACTEC instrument recording the time of the bottle was inserted, and the timing of flagging, the start time of the sample incubated until the appearance of flagging was recorded as TTP. The identification was done by Gram staining, followed by inoculation on a solid medium of 5% sheep blood and MacConkey. Identification was done by automated BD Phoenix system.

A miniVIDAS B.R.A.H.M.S analyzer performed procalcitonin level examination, according to the instructions in the kit. The lowest detection result was 0.05 ng/mL, and results >200 ng/mL were diluted with the serum of patients with normal PCT levels.

The Kolmogorov-Smirnov normality test was used to see the normality of the data, non-normally distributed quantitative variables were reported as median with their range, and their differences were evaluated with Mann-Whitney test, while normally distributed variables were reported as a mean ± SD and their differences were evaluated with the t-independent test. Correlation of variables was evaluated by Spearman correlation test in non-normally distributed and Pearson correlation test in normally distributed and $p<0.05$ was considered significant.

Ethical Clearance was obtained from the ethical commission of Adam Malik Hospital, Faculty of Medicine, the University of North Sumatra with number 410/TGL/KEPK FK USU-RSUP HAM/2016.

RESULTS AND DISCUSSION

A total of 229 patients with suspected bacteremia of which blood cultures were performed. The results were 58 samples (25.32%) with positive cultures and 171 samples (74.67%) negative. From the 58 samples with positive cultures, 46 (79.31%) were monomicrobial bacteria, 7 (12.07%) fungi, 3 (5.17%) contaminant bacteria (coagulase negative *Staphylococci* with TTP >24h, *Bacillus spp*. Diphtheroid), and 2 (3.45%) polymicrobial bacteria were found.

A total of 46 samples with monomicrobial growth were used as the samples for this study, which consisted of 21(45.7%) males, 25(54.3%) females. The age characteristics of this study were in the range of 20-78 years, Gram-positive bacteria were 26 (56.5%), and Gram-negative bacteria were 20 (43.5%) (Table 1).

The median TTP was 17.58 (range 6.33-58.83) hours, median PCT 7.47 (range 0.15 - 487.2) ng/mL, based on Gram staining as Gram-positive median 3.65 (range 0.15-65.58) ng/mL and Gram-negative 11.54 (range 0.46-487.2) ng/mL (Table 2).

The mean TTP of Gram-positive, Gram-negative, coagulase-positive *Staphylococci*, coagulase-negative *Staphylococci*, respectively, were 20.10±7.03, 19.62±13.88, 20.67±9.84, 19.98±6.05 hours (Table 3). The mean PCT of positive-coagulase *Staphylococci* and negative-coagulase *Staphylococci* respectively, were 11.75±21.64, 9.91±17.47 ng/mL (Table 4).

The positivity of blood cultures in this study was 25.32%. Another researcher found the same result with a quite low positivity ranging between 7.6% - 19.5%.[1,2,13-15] The low positivity rate in this study was probably caused by the amount of culture taken with only one bottle of 10 mL blood volume, and regardless of the history of antibiotic use, where on the Adam Malik Hospital is a tertiary referral hospital, in which the likelihood of patients already receiving treatment with antibiotics previously was quite large. In a study conducted by Dolma *et al*. who collected two bottles, there was a positive increase in the second bottle wherein the first bottle was 37% positivity but 63% in the second bottle.[16]

Three of the most common causes of bacteremia were *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Escherichia coli* (Table 1). The cause of bacteremia by Gram-based staining revealed a result of Gram-positive 26 (56.5%) and Gram-negative 20

Table 1. Bacteremia microbes

No	Microbe	Number
	Gram-positive	
1	*Staphylococcus epidermidis*	8
2	*Staphylococcus aureus*	7
3	*Staphylococcus hominis*	4
4	*Staphylococcus haemolyticus*	4
5	*Streptococcus pyogenes*	2
6	*Enterococcus faecalis*	1
		Total 26
	Gram-negative	
7	*Escherichia coli*	6
8	*Acinetobacter baumannii*	3
9	*Burkholderia cepacea*	2
10	*Klebsiella pneumoniae ssp. pneumonia*	2
11	*Pseudomonas aeruginosa*	1
12	*Shigella flexneri*	1
13	*Acinetobacter sp.*	1
14	*Enterobacter cloacae*	1
15	*Citrobacter farmer*	1
16	*Salmonella typhi*	1
17	*Serratia plymuthica*	1
		Total 20
	Total	46

Table 2. Time to positivity blood culture and procalcitonin level characteristics

Variable	N	Mean	Median	SD	Min	Max	Normality test (p-value)	Normality
TTP (hour)	46		17.58		6.33	58.83	0.019	Abnormal
PCT (ng/mL)	46		7.47		0.15	487.2	<0.001	Abnormal
TTP (hour)								
Gram-positive	26	20.10		7.03	11.83	42	0.099	Normal
Gram-negative	20	19.62		13.88	6.33	58.83	0.364	Normal
PCT (ng/mL)								
Gram-positive	26		3.65		0.15	65.58	0.018	Abnormal
Gram-negative	20		11.54		0.46	487.2	0.009	Abnormal
TTP (hour)								
Coagulase positive	7	20.67		9.84	11.83	42.0	0.356	Normal
Coagulase negative	16	19.98		6.05	13.67	40.0	0.296	Normal
PCT (ng/mL)								
Coagulase positive	7	11.75		21.64	0.15	60.24	0.168	Normal
Coagulase negative	16	9.91		17.47	0.17	65.58	0.96	Normal

(43.5%). The same result was found by Gopi *et al*. and Abe *et al*. studies.[13,17] The results was different from those found by Guo *et al*., in which Gram-negative was higher than Gram-positive.[11] The most common cause of sepsis was Gram-negative bacteria, but currently, the most common cause of sepsis is Gram-positive bacteria due to the increase of multi-drug resistant bacteria.[17]

The *Staphylococcus* group caused fifty percent (50%) of bacteremia cases in this study, with 16 (34.78%) cases caused by coagulase-negative *Staphylococci*. The finding showed no difference of

Table 3. Time to positivity, and PCT comparisons in bacteremia caused by Gram-positive bacteria and Gram-negative bacteria

Variable	n	$\bar{x} \pm SD$	$p.$
TTP (hour) [a)]			
Gram-positive	26	20.11 ± 7.04	0.888
Gram-negative	20	19.63 ± 13.88	
		Median	
PCT (ng/mL) [b)]			
Gram-positive	26	3.65	0.007*
Gram-negative	20	11.54	

Notes: a) t-independent test, b) Mann-Whitney test, * Significant

Table 4. Correlation between TTP and PCT in bacteremia patient

Correlation between variables	n	r	$p.$
TTP with PCT	46	-0.294	0.047*
TTP with PCT Gram-positive	26	-0.292	0.148
TTP with PCT Gram-negative	20	-0.206	0.348

TTP and PCT between coagulase-positive *Staphylococci* and coagulase-negative *Staphylococci* with consecutive p=0.839 and p=0.830 and by using Pearson correlation test. There was no relation between TTP and PCT neither on coagulase positive *Staphylococci* p=0.679 nor coagulase negative *Staphylococci* with p=0.736 (data not shown). Although the most common contaminant microbe was from the coagulase-negative *Staphylococci* group, many studies have shown that this bacteria group was the most common cause of infections in people with a low immune system and patients with intravascular and implant usage.[15,18-20] The virulence mechanism of coagulase-negative *Staphylococci* was less clearly known. Colonization of the polymer surface of medical equipment through the formation of biofilms in layers was alleged to be an important factor.[19] To determine whether coagulase-negative *Staphylococci* was the cause of bacteremia was difficult if the number of cultures performed used only one bottle, so some previous studies used TTP to differentiate bacteria from Gram-positive and contaminant groups by looking at TTP. Some researchers, including McGowan *et al*., concluded that Gram-positive bacterial blood culture detection was faster than Gram-positive contaminant bacteria (15.5 hours vs. 25.0 hours).[21] Ruimy *et al*., obtained a median of 14-hours TTP for *S.aureus* while 26-hours for coagulase-negative *Staphylococci*. TTP of 2 - 9 hours had 83.3% probability that the growing bacteria was *S.aureus*, and vice versa if TTP was ≥ 18h, a 90.8% chance of the growth was coagulase-negative *Staphylococci*.[22] A prior research by Garcia-Vazquez *et al*., showed that bacteremia caused by coagulase-negative *Staphylococci* with TTP of <16 hours was strongly suspected bacteremia.[23] Kassis *et al*. claimed that to distinguish coagulase-negative *Staphylococci* as a cause of bacteremia or just as a contaminant was when coagulase-negative *Staphylococci* with TTP > 20 hours.[24]

Coagulase negative *Staphylococci* with TTP > 24 hours excluded from the study as being considered bacterial contaminants. Statistical analysis showed no significant differences in both TTP and PCT between coagulase-positive *Staphylococci* and coagulase-negative *Staphylococci*.

In this study, there was no significant difference between Gram-positive and Gram-negative TTP as the mean TTP for Gram-positive was 20.11±7.04 hours, and Gram-negative was 19.63 ± 13.88 hours (Table 3). These results were consistent with the results of a study conducted by Gopi *et al*. in which the mean TTP value of Gram-positive bacteria was 19.33 hours, and Gram-negative was 19.06 hours. Different results were obtained by Samir *et al*, with a mean TTP for Gram-negative rods was 12.8 hours while for Gram-positive was 19.0 hours.[13,14] This difference was thought to be influenced by several factors, including the number of bacteria, species of microorganisms, blood volume inserted into the culture bottle, the source of infection, previous antibiotic treatment and clinical characteristics of the

patient. Species of microorganisms were also one important factor that affected bacterial growth time.[6]

In this study, the researchers found that the levels of PCT produced by Gram-negative bacterial infections were significantly higher than those by Gram-positive bacterial infection with p<0.05 (Table 3). Procalcitonin ability to differentiate infections by Gram-positive and Gram-negative bacteria was found in several previous studies where PCT levels were significantly higher in bacteremia caused by Gram-negative bacterial infections compared to Gram-positive.[11,25-28] Differences in PCT production were due to differences in interactions between Gram-positive and Gram-negative bacteria with the host cells, involving lipoteichoic, peptidoglycan and Lipopolysaccharide (LPS) acids and Pathogen-Associated Molecular Pattern (PAMPs) differences, involving different TLRs, expressed in human cells. Gram-positive bacteria will activate the TLR2 pathway, whereas Gram-negative bacteria activate the TLR4 pathway which will result in differences in cytokine production such as interleukin-1β, interleukin-6 (IL-6), and α-factor necrosis factor, which ultimately stimulates transcription of calcitonin- mRNA and release PCT from various body tissues.[11,25,29] Gram-negative bacteria can produce endotoxins in which this endotoxin may also be released when the cell dies, which causes PCT levels to remain high. In bacteremia patients, PCT levels also differ according to species of the bacteria.[30]

The results of this study showed three samples with very high PCT levels where the cultures were Gram-negative bacteria from the *Enterobacteriaceae* group, *Escherichia coli*, *Shigella flexneri*, and *Citrobacter farmeri* with PCT levels of 487.2 ng/mL, 482.2 ng/mL and 252.8 ng/mL, respectively. This was in line with previous studies in which higher levels of PCT were attributed to *Enterobacteriaceae* gram-negative bacteria compared with the non-fermenter Gram-negative bacteria.[25,30] Watanabe *et al*. in his research found that ESBL bacteria positive resulted in higher PCT levels than ESBL negative bacteria.[27] In this study, *Escherichia coli* bacteria with ESBL positive resulted in a wide variation in PCT levels, one with a very high PCT level of 487.2 ng/mL and one with levels of 0.73 ng/mL and no appropriate reason was found to explain these findings.

The correlation between TTP and PCT was tested by Spearman correlation test. There was a significant correlation (p <0.05) between TTP and PCT, with r = - 0.294. The correlation value described the inverse relationship, meaning that the smaller TTP was, the bigger PCT, but the correlation was weak (Table 4). This was following the results of research conducted by Hattori *et al*., and Nieuwkoop *et al*. where PCT accurately predicted bacterial counts and the presence of bacteremia in urinary tract infection with fever patients.[2,31] In the group of bacteria divided by Gram staining, neither Gram-positive nor Gram-negative bacteria showed a significant relationship between TTP and PCT, in which the result for Gram-positive was p=0.148 with r = - 0.292 and Gram-negative was p=0.348 with r = - 0.206 with a weak correlation (Table 4).

The results of this study on the relationship between TTP and PCT indirectly reinforced the notion that PCT examinations could be used to distinguish between contamination and actual bloodstream infections by coagulase-negative Staphylococci.[32] Given the initial number of bacteria in the inoculum affecting the TTP value. The short TTP value described the number of more pathogens in blood culture samples, as well as some studies showing that shorter TTP values were associated with a higher risk of death at bacteremia patients. Researchers concluded that the shorter the value of TTP, the more bacteria that would stimulate the production of PCT. The relationship between TTP and PCT could support the idea that TTP values could be used to predict bacteremia severity.[3,6]

Limitations of this study were samples for blood cultures taken used only one bottle of 10 mL volume, due to the difficulty of obtaining consent from the patient. Previous antibiotic usage history could not be traced where the possibility of antibiotics before admission to the hospital was considerable.

CONCLUSION AND SUGGESTION

There was a significant relationship between TTP blood cultures with PCT levels in patients with bacteremia with negative correlation. This relationship showed that the shorter value of TTP, the greater the PCT level will be. Significantly higher levels of PCT in cases of bacteremia were more likely to be caused by Gram-negative bacteria than Gram-positive bacteria. Researchers suggest that further research should be conducted on the correlation between TTP with the level of PCT based on the species of the bacteria.

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