Analysis of Blood Culture Profile and Factors Related to Microbial Patterns and Antibiotic Resistance in Intensive Care Unit

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Introduction:- Bloodstream infection is an infectious disease characterized by the presence of live bacterial or fungal microorganisms in the bloodstream, as evidenced by positive blood cultures. These pathogens have an important role in infection, especially in the intensive care unit (ICU). Although infection is not the most common cause of mortality in ICU care, infection is confirmed to be associated with increased hospitalization and high treatment costs.

Objective: This study aims to determine the profile of blood culture, the factors that have a bearing on the results, and the description of antibiotic resistance in patients at Haji Adam Malik General Hospital.

Method: This study is a study using secondary data from patients in ICU Haji Adam Malik General Hospital in 2019 - 2020 conducted by blood culture.

Results: This study included data from 52 patients who were recorded between 2019 – 2020 and underwent blood culture. There are 50% women and men each with an average age of 54,69 years. Based on the acquisition of a positive blood culture in terms of the day of admission, found 33 people (61.4%) positive patients after passing 48 hours. The highest morphology was Gram negative rods, 52.8% with the most species, *Klebsiella pneumoniae* ESBL positive, and found Carbapenemase-producing bacteria (5.5%). The most common Gram-positive bacterium is *Staphylococcus aureus* (15%), and half is suspected MRSA.

Conclusion: Most types of bacteria found in ICU patients in Haji Adam Malik General Hospital are Gram-negative rod bacteria, with the time it was found above 48 hours after entering the hospital. The picture of antibiotic resistance is in line with the bacteria found with the property of drug resistance. Preventive measures are needed to prevent patients from the possibility of transmitting these microorganisms.

Keywords:- Culture, Blood, Microorganisms, Resistance, ICU.

I. INTRODUCTION

A bloodstream infection (BSI) is an infectious disease characterized by the presence of live bacterial or fungal microorganisms in the bloodstream, as evidenced by a positive blood culture.[1] BSI is a frequent and life-threatening event in the hospital environment, where it is associated with a high mortality of around 40-60%. Severely ill patients are predisposed to getting BSI, which occurs in about 7% of patients in the first month of treatment in the intensive care unit (ICU).[2]

Recently, there has been a shift towards resistant strains in recent years, such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), extended - spectrum beta-lactamases (ESBLs), carbapenems - resistant Enterobacteriaceae (CRE), colistin resistant acinetobacter, and fluconazole-resistant Candida spp. These pathogens have an important role in infection especially in the ICU. Although infection is not the single most common cause of mortality in ICU patients, it is confirmed that infection is associated with increased length of stay and high hospital costs. Information and scientific development regarding clinical epidemiology, microbiological etiology, and pathophysiology of disease can certainly help understand the concept of infection control, and ultimately the appropriate use of antibiotics.[3]

This study aims to determine the profile of blood culture, the factors - factors related to the results, as well as the description of antibiotic resistance in patients with Haji Adam Malik General Hospital.

II. METHOD

This study is a descriptive analytic study with a cross-sectional approach. This research was conducted in the ICU of Haji Adam Malik General Hospital Medan. This study started from March 2020 with secondary data meeting the criteria taken from treatment in 2019 - 2020. The research subjects were secondary data of all patients who were treated in the ICU ward of Haji Adam Malik General Hospital Medan and blood cultures were performed in the ICU of Haji Adam Malik General Hospital Medan.

The number of subjects included in this study were 52 people. The inclusion criteria of the patient was an ICU patient at Haji Adam Malik General Hospital, at least 18 years old, and a blood culture was performed. There were no exclusion criteria in that study. Subjects were selected by consecutive sampling.

In addition to demographic characteristics in the form of age and sex, some of the variables examined include conditions of bloodstream infections such as bacteremia and fungemia, bacterial patterns described by Gram and species identification, and patterns of antibiotic resistance. A history of central venous catheter placement and mechanical ventilation was also seen in the patient.

This research process has passed the ethical clearance test from the Medical Research Ethics Commission of the University of Sumatra Utara and obtained a research permit from the institution where the research was conducted, namely the Haji Adam Malik General Hospital Medan.

III. RESULT

This study includes data from 52 patients who were recorded between 2019 – 2020 and underwent a blood culture process. There are 26 people (50%) women and 26 samples (50%) are men. The majority of the population in this study were adults, namely 37 people (69.8%) with an average (mean) age of 54.69 years (Table 1).

Table 1. Frequency distribution of research subjects by gender

Subject Characteristics	N	%
Gender		
Male	26	50
Female	26	50
Age (WHO Classification)		
Adult (20 – 60 years old)	37	69,8
Elderly (> 60 years old)	15	28,3

Elderly Based on positive blood culture obtained from the day of admission, 33 (61.4%) patients were positive after 48 hours of treatment, while the rest were under 48 hours. It is included in the category of bloodstream infection with onset or hospital-acquired, because it is identified after 48 hours of admission.

In this study, it was found that 52 blood cultures were collected with positive results of microorganism growth, where all samples obtained bacterial growth (100%). Fungal growth was only found in one sample (1.9%). Multiple infections were found in two samples, namely infection with two types of bacteria (Escherichia coli ESBL positive and Klebsiella pneumoniae ESBL positive), and infection with bacteria and fungi (Enterococcus faecium and Candida lucitanae)(Table 2).

Based on Gram staining, it was found that there were almost equal numbers of Gram negative bacteria (52.8%) and Gram positive bacteria (47.1%). The most morphology was Gram negative rods, which was 52.8% with the most species being *Klebsiella pneumoniae ESBL positive* with 11 samples.

Table 2. Blood Culture Result

Results		%
Based on Blood Culture Results		
- Bacterimia	52	100
- Fungemia	1	1,9
- Multiple infections	2	
Based on Gram Stains (n = 53)		
- Gram Positive	25	47,1
- Gram Negative	28	52,8
Based on Bacterial Morphology (n = 53)		
- Coccus Gram Positif	23	43,3
- Coccus Gram Negatif	0	0
- Batang Gram Positif	2	3,7
- Batang Gram Negatif	28	52,8
Based on Bacterial Species (n = 53)		
- Acinetobacter baumanii	3	5,6
- Acinetobacter baumanii Carbapenemase positif	1	1,8
- Burkholderia cepacia	1	1,8
- Burkholderia pseudomallei	1	1,8
- Enterobacter cloacae	2	3,7
- Escherichia coli	1	1,8
- Escherichia coli ESBL positif	5	9,4
- Klebsiella pneumoniae ESBL positif	11	20,8
- Psedomonas aeruginosa	1	1,8
- Psedomonas aeruginosa Cabapenemase positif	2	3,7
- Actinomyces odontylicus	1	1,8
- Corynebacterium striatum	1	1,8
- Enterococcus faecium	4	7,5

-	Staphylococcus aureus	4	7,5
-	Staphylococcus aureus cefoxitin positif (Susp MRSA)	4	7,5
-	Staphylococcus capitis	1	1,8
-	Staphylococcus epidermidis	3	5,6
-	Staphylococcus epidermidis Cefoxitin +	1	1,8
-	Staphylococcus haemolyticus	2	3,7
-	Staphylococcus hominis	2	3,7
-	Staphylococcus hominis Cefoxitin positif	2	3,7
Based on Fungal Species			
-	Candida lusitaniae	1	1,8

Based on the types of Gram-positive bacteria, the most common genus found was Gram-positive cocci with the most species being Staphylococcus aureus, which was about 8 samples (15%). Four of the eight samples of Staphylococcus aureus had positive Cefoxitin screening test results so that they were suspected to be MRSA.

From 44 patients who had CVC installed, it was found that the number of Gram negative and Gram positive bacteria was almost the same, namely 45.46% and 54.54%, respectively. The results of the relationship between two categorical variables obtained a P value of 0.308 from Fisher's test, there is no relationship between CVC installation and the incidence of Gram positive bacteria (Table 3).

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Table 3. Bacterial Patterns Based on the Use of CVC

	Yes	No	P value
Gram Positive	20	5	
Gram Negative	24	3	0,308
Total	44	8	

Of the 48 patients who were on a ventilator, it was found that the number of Gram negative and Gram positive bacteria was almost the same, namely 45.8% and 54.2%, respectively. The results of the relationship between the two categorical variables obtained a P value of 0.278 from Fisher's test, which means that there is no relationship between ventilator installation and the incidence of Gram-negative bacteria (Table 4).

Table 4. Bacterial Patterns Based on the Use of Ventilators

	Yes	No	P value
Gram Positive	22	3	
Gram Negative	26	1	0,276
Total	48	4	

Of the 53 types of bacteria obtained on blood cultures, it was found that the treatment was below 48 hours and above 48 hours, the most Gram-negative bacteria were found in the treatment above 48 hours. The results of the relationship between the two categorical variables obtained a P value of 0.081 from the Chi Square test. There was no relationship between the time of admission and the incidence of Gram-positive bacteria (Table 5).

Table 5. Bacterial Patterns Based on Admission

	Blood Culture		P value
	<48hour	**>48hour**	
Gram Positive	12	13	
Gram Negative	7	21	0,081
Total	19	34	

There are variations in the distribution of germ patterns based on the patient's diagnosis. The most bacteria were found, namely Gram-positive in diseases of the urogenital system, and the most Gram-negative in diseases of the nervous system and infections. One fungal infection was found in one patient with acute peritonitis.

There are 33 types of antibiotics recorded that have been tested. Some of the most common antibiotics tested were Ciprofloxacin (51 times), Tigecycline (43 times), Gentamycin (46 times), and Ampicillin Sulbactam (46 times). The minimum tests were antibiotics Azithromycin (1 time), Cefixim (1 time), Chloramphenicol (1 time), Cotrimoxazole (2 times), and Penicillin (3 times) (Table 7). The antibiotics with the highest sensitivity level were Cefoperazone and Cefixim, with 100% of a single examination. Antibiotics with the highest sensitivity after being examined in more than half of the samples were Amikacin (88.9%), Meropenem (85.7%), Tigecycline (91.5%). Antibiotics with the highest resistance level were Azithromycin, Chloramphenicol, Penicillin with a value of 100%. Antibiotics with the highest resistance after being examined in more than half of the samples were Ampicillin (92.6%) and Cefazolin (89.7%).

IV. DISCUSSION

The global prevalence of bloodstream infections is very difficult to assess because of the different patient populations and the different types of hospitals. In this study, it took a large time range to meet the needs of the number of samples that met the positive criteria. In Europe alone the prevalence ranges from 2.3 to 10.8 percent, which means that from 100 people cultured the probability of getting a patient with positive bloodstream infection is 2 to 10 people.[1]

Table 7. Antibiotic Sensitivity Test Results

Antibiotic Type	Sensitivity Test Results n (%)			
	S	I	R	SDD
Amikacin (n = 27)	24 (88,9)		3 (11,1)	
Amoxicillin (n = 22)	3(13,6)		19(86,4)	
Ampicillin (n = 27)	2(7,4)		25(92,6)	
Ampicillin Sulbactam (n = 46)	10(21,7)	2(4,3)	34(73,9)	
Azithromycin (n = 1)			1(100)	
Cefalexin (n = 15)	1(6,7)		14(93,3)	
Cefazolin (n = 29)	3(10,3)		26(89,7)	
Cefixim (n = 1)	1(100)			
Cefotaxim (n = 6)	5(83,3)	1(16,7)		
Ceftazidime (n = 31)	11(35,5)	1(3,2)	19(61,3)	
Ceftrizxone (n = 28)	5(17,9)	1(3,6)	22(78,6)	
Cefuroxime (n = 20)	4(20)		16(80)	
Ertapenem (n = 20)	18(90)	1(5)	1(5)	
Cefepime (n = 32)	15(46,9)	1(3,1)	13(40,6)	3(9,4)
Cefoperazone Sulbactam (n = 3)	2(66,7)		1(33,3)	
Chloramphenicol (n = 1)			1(100)	
Ciprofloxacin (n = 51)	8(15,1)	2(3,8)	41(80,4)	
Clindamycin (n = 20)	7(35)	1(5)	12(60)	
Cotrimoxazole (n = 2)	1(50)		1(50)	
Erythromycin (n = 25)	7 (28)		18(72)	
Gentamycin (n = 46)	19(41,3)		27(50,9)	
Levofloxacin (n = 22)	4(18,2)		18(81,8)	
Meropenem (n = 28)	24(85,7)	1(3,6)	3(10,7)	
Netilmicin (n = 35)	14(40)	4(11,4)	17(48,6)	
Penicillin (n = 3)			3(100)	
Tigecycline (n = 47)	43(91,5)		4(8,5)	
Tetracycline (n = 45)	15(33,3)		30(66,7)	
Vancomycin (n = 25)	23(92)		2(8)	
Cefoperazone (n = 4)	4(100)			
Trimethoprim Sulfamethoxazole (n=42)	21(50)		21(50)	
Aztreonam (n = 22)	1(4,5)		21(95,5)	
Fosfomycin (n = 25)	15(60)	1(4)	9(36)	
Moxifloxacin (n = 18)	4(22,2)	1(5,6)	13(72,2)	

Note: S (sensitive); I (intermediate); R (resistant); SDD (Sensitive Dose Dependent)

It was found in this study that the sexes were balanced in number between men and women, namely 26 people (50%) each. In a study by Christaki & Giamarellos-boubulis in 2014, more of this disease was found in men with old age or very young age. In terms of age, the largest age group in this study was 20-60 years (69.8%) with a large range of variation, and the average age was 54.69 years. In some countries, including the classification by the Ministry of Health in 2009, the average age group has been classified as old age.[4]

Based on the time of admission, in this study, 61.4% of patients were positive for blood culture after 48 hours. The group of bloodstream infections can be divided into hospital-acquired infections (<48 hours), and out-of-hospital onset (<48 hours). This indicates the possibility that the infection originated in the hospital.

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The use of CVC is routine in the ICU, due to the patient's clinical condition and the need to include various types of therapy. In this study, approximately 84.6% of patients had CVC installed and were positive for bacteremia. While the remaining 13.4% did not have a CVC installed due to access to catheterization elsewhere, for example in this case, patients with chronic kidney disease. Invasive measures are one of the risk factors for bloodstream infections because they provide a port d'entree for microorganisms. Rapid catheter change can reduce bloodstream infections.[1]

It was found that 48 people (92.30%) in this study were using ventilators with various microorganisms. According to Basetti in his study of bloodstream infections in the ICU, the biggest risk factors for bloodstream infections are length of stay, use of mechanical ventilation, surgical therapy, renal replacement therapy, and use of intravascular catheters. This statement is in line with the phenomenon found in this study where positive blood culture results were found in the study patients with an average length of stay of 8 days, the use of mechanical ventilation around 92.30%, the use of CVC 84.6%, some undergoing surgical therapy and hemodialysis.[2]

The results of blood culture on all positive samples showed that all of them were infected with 92.30 bacteria, of which 52.8% of the samples were Gram-negative rods. In this study, the most common types of bacteria found were Gram negative bacteria, this is in line with the pattern of changes in bloodstream infections which used to be the majority of Gram positive.[1] According to Basetti, of the most isolated Gram negative bacteria, Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumanii , and Pseudomonas are often isolated in patients. This is in line with this study where the previously mentioned microorganisms were among the samples obtained. Followed by the genus Staphylococcus with the most species in this study, namely Staphylococcus aureus. And the presence of Candida spp infection in one of the samples. This is in line with Basetti's statement regarding microorganisms in ICU patients, and shows a similar trend in various locations.

One patient had multiple bacterial and fungal infections (Enterococcus faecium and Candida lucitanae). The fungemia that occurred in the sample was a study that suffered from acute peritonitis. According to Enoch, several factors causing invasive fungal infections are the use of antineoplastic and immunosuppressants, broad - spectrum antibiotics, prosthetic devices and grafts, as well as aggressive surgery. However, according to Wawrysiuk in a 2018 case report, Candida lusitaniae infection is a rare infection. This fungus itself is often resistant to Amphotericin B. In the case report, it was reported that the infection in the patient occurred intraperitoneally after laparoscopic surgery. In another study conducted by Rodolico, he found 66 cases of intra-abdominal infection by Candida spp during a 5 year study.[6]

Based on the number of microorganisms isolated, the most microorganisms found in this study were Klebsiella pneumonia (20.8%), Staphylococcus aureus (15%), and Escherichia coli (11.2%). This is almost similar to the study by Edwardson although in a different order, where the most bacteria isolated from blood was Staphylococcus aureus, followed by Enterococcus spp, Serratia spp, and Klebsiella spp.[7]

The incidence of Carbapenemase-producing Gram negative bacteria and Extended Spectrum Beta Lactamase (ESBL) is a threat in the ICU. Most Klebsiella pneumonia and Escherichia coli are resistant to ampicillin due to the production of plasmid-mediated beta lactamase which can inactivate broad-spectrum cephalosporins, penicillins, and aztreonam.[8] In this study alone, 3 samples (5.5%) of patients with carbapenemase-producing Gram-negative rods were found, and 16 (30.2%) Gram negative ESBL-producing bacteria. It is known that the use of a ventilator has a risk of contracting a person with positive ESBL enterobacteriaceae, namely a group of Gram-negative rods of about 5-20%. The most common microorganisms isolated were Pseudomonas aeruginosa and Staphylococcus aureus, but enterobacteriaceae such as Eschericia coli and Klebsiella also reached almost 20%, in line with this study where Klebsiela infection reached 20.8%, and when accumulated with other enterobacteriaceae it reached 41.2%. The high number of ESBL-producing Gram-negative rods in the ICU where there is an average resistance to third-generation cephalosporins causes the Carbapenem group to be suggested as the drug of choice for infection, but the presence of Carbapenemase-producing Gram-negative bacteria makes this a concern.[9]

The number of ESBL-producing bacteria in this study was 30.2 percent. In a study conducted in France, ESBL colonization increased with the length of stay in the ICU, i.e., an average period of more than five days, although not all patients who had ESBL colonization developed an infection. Klebsiella pneumonia itself is a bacterium that is a flora commonly found in humans. Some isolates that were rarely found in this study were Burkholderia cepacia, Burkholderia pseudomallei, Actinomyces odolynticus, Corynebacterium striatum, and Staphylococcus capitis where these bacteria were found each of the 52 samples examined.

Burkholderia pseudomallei in the study sample was found in a 59 year old man with diabetes mellitus who suffered from pneumonia. This bacterium is a saprophytic microorganism that is widely found in tropical soils and stagnant water. The risk factors for this disease are diabetes, chronic alcoholism, and chronic kidney failure, and age over 50 years. An article by Abidin in 2017 about a case report of a patient with acute pneumonia due to Burkholderia pseudomallei found this infection in post-traumatic ICU patients where trauma was suspected as a port d'entree mechanism. In the case of culture research, it was carried out on the sixth day of treatment, so that the criteria for this is a matter of debate.[10]

In the calculation to determine the relationship between hospital admissions, CVC installation, ventilator installation, with a cumulative pattern, it was found that there was no significant relationship. This is thought to be due to the heterogeneity of the sample so that there are many possible biases. However, from the search for the types of germs, it can be seen that the trend is in line with the various studies as described.

There are 33 types of antibiotics recorded that have been tested. Some of the most common antibiotics tested were Ciprofloxacin (51 times) with a sensitivity of 15.1%, Tigecycline (43 times) with a sensitivity of 91.5%,

Gentamycin (46 times) with a sensitivity of 41.3%, and Ampicillin Sulbactam (46 times) with sensitivity of 21.7%. From Thakuria's statement in his research regarding antibiotic resistance in ventilator users, it was found that there was a high sensitivity to the Tigecyline and Polymyxin B groups against Gram-negative isolates, and Vancomycin against Gram-positive isolates. In that study it was also observed that the use of cephalosporins as first-line therapy is very common despite the fact that their performance is poor. In this study, the level of resistance to the cephalosporins themselves were Cefalexin (93.3%), Cefazolin (89.7%), Ceftazidime (61.3%), Ceftriaxone (78.6%), Cefuroxime (80%), while none were found. resistance to Cefotaxime and Cefixim. Cefixim alone was only examined once in patients with positive Burkholderia pseudomallei cultures.[11]

In Gram positive isolates, the problem of MRSA is also a matter of concern. The use of Vancomycin has also increased because of this. In this study, the sensitivity of vancomycin was 92%. According to Basetti from Tumbarello's writings, there was an increase in mortality due to MRSA due to inadequate empiric antibiotics given.[2] Due to the high mortality and frequent finding of pathogen isolates which are considered difficult to treat according to various studies, as well as the large number of patients with various dangerous comorbidities in the ICU, preventive measures must be taken to prevent this from happening. Reducing transmission is one way to control outbreaks of pathogenic MDR bacteria. There have been many protocols regarding many safe ways such as standard catheter insertion and management of care in patients in the ICU that can reduce the incidence of bloodstream infections in the ICU.

V. CONCLUSION

The most common types of bacteria found were Gram-negative rods, followed by Gram-positive cocci, with the highest number of bloodstream infections found after 48 hours of treatment. It is necessary to take preventive measures and strengthen protocols in all actions to prevent the transmission of dangerous pathogens, and periodic evaluation and monitoring are necessary to protect patients and health workers in the ICU.

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