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Association between the Antibiotic Factors and the Development of Bacterial Resistance in Bloodstream Infections in the Critical Care Unit

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Abstract

The irrational use of antibiotics is one of the factors in the emergence of Multidrug-resistance (MDR) bacterial infections, which is estimated to continue to increase patient's mortality until 2050. This study aims to analyse the factors that influence the development of bacterial resistance in bloodstream infections in Critical care settings at a tertiary hospital in Indonesia. This study is an observational retrospective study with Case-control research method. This research uses the electronic medical record (EMR) data of the inpatients in the Intensive Care Unit and High Care Unit at Dr. Soetomo Academic Hospital, Surabaya, Indonesia, from July 2023 to June 2024. Total of 97 patients with bloodstream infection by MDR bacteria detected were recruited as the sample group. Patients with bloodstream infection but no resistance detected during the hospitalization period were recruited as the control group with 1:1 proportion. There were 172 antibiotic prescriptions in the sample group and 183 in the control group. It was found that the factors that influence the development of resistance were prophylactic antibiotic used in non-surgical (adjusted OR = 9.187; CI 95% = 1.9-44.37; p = 0.006), the use of endotracheal tube (adjusted OR = 2.30; CI 95% = 1.37-3.86; p = 0,002) and immune suppression medication (adjusted OR = 2.709; CI 95% = 1.3-5.65; p = 0.008). This study indicates that in Critical care population of Dr. Soetomo General Academic Hospital, the use of non-surgical prophylaxis antibiotics, endotracheal tube devices, and immune suppression caused by medications were significant factors that increase bacterial resistance in bloodstream infection.

Keywords: Hospital Acquired Infection, Bloodstream Infection, Antibiotic Use, Multidrug-resistant, Critical Care Unit

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INTRODUCTION

Antimicrobial resistance (AMR) has emerged as a significant worldwide health concern in the 21st century with an estimated 4.71 million (95% UI 4.23-5.19) deaths were linked to bacterial antimicrobial resistance (AMR), including 1.14 million (1.00-1.28) deaths directly attributable to bacterial AMR.[1,2] According to the 2021 WHO report, Bloodstream Infection (BSI) itself has a mortality rate of 15-30% and it is found that in Indonesia, BSI that is caused by MDR bacteria increase the mortality rate by 29.7% compared to the patients without infection in the Critical care settings.[3,4]

Resistance is a natural response from the bacteria as an organism to preserve themselves in the exposure of antibiotics.[5] Other factors that influence the risk of MDR colonization, bacterial invasion, and patient's immune status may also affect the emergence of bacterial resistance which include: 1. Length of stay; 2. Treatment area; 3. Comorbidities; and 4. Environment of care.[6] The environment of care like Intensive Care Units (ICU) and High Care Units (HCU), have several factors that influence infection: 1. Use of invasive devices; 2. Critical illness; 3. Comorbidities; 4. Nutrition; and 5. Therapeutic factor.[6-9] Mechanism of action, indication, dosage, frequency, duration of therapy, number of antibiotics used may also have influence the development of bacterial resistance.[6,8,10,11]

Some studies have shown correlation between antimicrobial use and the development of resistance.[6,12] This study aims to further analyse the factors that influence the development of bacterial resistance in bloodstream infections in Critical care settings at a tertiary hospital in Indonesia. The critical care factors included antibiotic administration, prophylactic usage, empirical treatment, definitive therapy, and its interactions with comorbidities found in critical care settings such as malignancy, diabetes mellitus, surgical/trauma case, kidney failure, burn, medical device, and immunosuppression in the process of developing bacterial resistance in bloodstream infection.

MATERIALS AND METHODS

Data source

This study is an observational retrospective study which uses Case-control research model that aims to determine the causal relationship between antibiotic factors with the emergence of resistance in bacteria that cause bloodstream infections. We conducted a retrospective study using routinely available hospital admission and microbiological datasets in Dr. Soetomo Academic Hospital from July 2023-June 2024. Dr. Soetomo Academic Hospital is a tertiary hospital situated in East Java, Indonesia. The microbiology laboratory used the BD Phoenix TM Automated Identification and Susceptibility testing system to determine microorganism species and resistances. Both the clinical and microbiological data were electronically recorded in the Electronic Medical Record (EMR) system.

Methods

Study population

To reduce variation between sample, only 18 years old and older Critical care units (ICU and HCU) patients' data were extracted. The sample population was patients with bloodstream infections and have blood culture examination in both ICU and HCU at Dr. Soetomo Academic Hospital from July 2023-June 2024. The types of resistance evaluated in this study are Methicillin-resistant *Staphylococcus aureus* (MRSA), Extended-spectrum Beta-lactamase producing *Enterobacterales* (ESBL-E), Carbapenem-resistant *Enterobacterales* (CRE), Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), Carbapenem resistant *Acinetobacter baumannii* (CRAB), and Extended drug-resistant microorganism (XDR) since no other type of resistance were found from the EMR during the duration of data collection. Only the first drug resistant bacteria from blood culture for each patient were recorded in this study.

Sampling procedure used was the total sampling method. Patients in Critical care unit with bloodstream infection but no resistance developed during the duration of hospitalization were

recruited as control group with 1:1 proportion to the sample. Only the first positive blood culture result was recorded in this study for the control group, however all the blood cultures during hospitalization must not have any resistance detected for the patient to be eligible as a control. The sample group later shall be referred as Drug-resistant (DR) group while the control group is the non-Drug-resistant (Non-DR) group.

The patients who had positive drug-resistant bacteria from blood culture which performed ≤48 hours of hospitalization were excluded. The patient with incomplete data, referred to other hospital or discharged due to the patient's or family request also not included in this study. The data collection spans from July 2024-October 2024.

Antimicrobial factors

The infection status and choice of treatment were extracted as secondary data from EMR and were determined by the physician or specialists in charge using local treatment guidelines commonly used in Dr. Soetomo Academic Hospital.[13-37] Only intravenous antibiotic usage was evaluated in this study since it was the dominant route of administration in both the sample and control population found during the duration of data collection. A patient may have more than 1 antibiotic prescription and each antibiotic prescription was treated as separate data. Independent variable in this study was the type of antibiotic, indication of use, dose, frequency, duration of exposure, antibiotic combination, number of antibiotics uses, and total duration of therapy before the resistance occur. All the intravenous antibiotic prescriptions before the resistance occur were included without exception in the DR group, while for the non-DR group all the intravenous antibiotics administered during the hospitalization period was taken for the analysis. The dependent variable in this study is the development of bacterial drug resistance. The antibiotic indication was separated into: 1. Surgical prophylaxis; 2. non-surgical prophylaxis; 3. Empirical therapy; 4. Definitive therapy.[38,39] Prophylaxis was defined as the use of antibiotic without any sign of infections, which is further separated into surgical and non-surgical prophylaxis.[38,39] Surgical prophylaxis defined as a prophylaxis given 30 minutes-1 hours before surgical procedure up to maximum 24 hours or specifically 48 hours for thoracic surgery procedure while other prophylaxis uses were classified as non-surgical prophylaxis.[38-41] Empirical therapy group was defined as the use of antibiotics in a patient with clear sign of infection but no definitive microbiological culture result while definitive therapy group was for the antibiotics which is used in accordance of microbiological culture result.[38] The status of infection was determined in accordance to the data recorded in EMR.

Antibiotic dosage and frequency were analysed as parametric data and classified further into standard dose/frequency or adjusted dose/frequency in accordance to the Lexi-Drugs Multinational antimicrobial monograph which is used in Dr. Soetomo Academic Hospital as guideline. Standard dose and standard frequency were defined if the dosage/frequency used in the therapy in 24 hours is the standard dose/frequency of that antibiotic for systemic infection in a patient without renal or liver failure. Other dose or frequency used were defined as adjusted dose or frequency group.[15-37] Duration of exposure for each antibiotic prescription was analysed as parametric data. Combination of therapy was recorded in accordance to the number of antibiotics used in the same time. No more than 3 antibiotic combination were found in this study, so it is classified into 3 groups: 1. Monotherapy; 2. combination of 2 antibiotics; and 3. combination of 3 antibiotics. The number of antibiotics were recorded as the total number of antibiotics used for each patient during the hospitalization period. The length of therapy counted from the beginning of antibiotic therapy was given until the day bacterial resistance detected from the blood culture for the DR group or the entire course of antibiotic therapy during hospitalization for the non-DR group. Length of therapy was divided into ≤7 days; 8-14 days; and >14 days in accordance to WHO guideline for systemic infection (sepsis).[14]

Critical care variable recorded in this study such as age, gender, comorbidities, immune suppressive treatments, invasive device, and surgery status were analysed separately. The comorbidities found in this study were diabetes mellitus, cerebrovascular accident (CVA), liver disease. renal disease, and burn patients.

Table 1. Summary of blood culture result from the patients admitted in Critical Care Unit at Dr. Soetomo Academic General Hospital July 2023-June 2024

Blood Culture result	DR (N = 97)	%	Non-DR (N = 97)	%
Gram stains				
Gram-negative	93	95.88%	59	60.82%
Gram-positive	4	4.12%	38	39.18%
Species				
Escherichia coli	37	38.14%	11	11.34%
Klebsiella pneumoniae	31	31.96%	7	7.22%
Acinetobacter baumannii	14	14.43%	10	10.31%
Pseudomonas aeruginosa	6	6.19%	14	14.43%
Proteus mirabilis	4	4.12%	0	0.00%
Staphylococcus aureus	4	4.12%	28	28.87%
Klebsiella aerogenes	1	1.03%	0	0.00%
Acinetobacter species	0	0.00%	1	1.03%
Aeromonas species	0	0.00%	2	2.06%
Burkholderia cepacia	0	0.00%	2	2.06%
Citrobacter freundii	0	0.00%	2	2.06%
Enterobacter cloacae	0	0.00%	4	4.12%
Enterobacter hormaechei	0	0.00%	1	1.03%
Enterococcus faecalis	0	0.00%	5	5.15%
Enterococcus faecium	0	0.00%	1	1.03%
Morganella morganii	0	0.00%	1	1.03%
Pseudomonas oryzihabitans	0	0.00%	1	1.03%
Salmonella species	0	0.00%	1	1.03%
Serratia marcescens	0	0.00%	1	1.03%
Staphylococcus coagulase-negative	0	0.00%	2	2.06%
Stenotrophomonas maltophilia	0	0.00%	1	1.03%
Streptococcus mitis/oralis	0	0.00%	1	1.03%
Streptococcus pyogenes	0	0.00%	1	1.03%
Type of Resistance				
ESBL-E	55	56.70%		
XDR	28	28.87%		
CRE	7	7.22%		
MRSA	4	4.12%		
CRAB	2	2.06%		
CRPA	1	1.03%		

DR: Drug-resistance group; Non-DR: Non-Drug-resistant group; ESBL-E: Extended Spectrum Beta-lactamase producing *Enterobacterales*; XDR: Extended Drug-resistant microorganism; CRE: Carbapenem-resistant *Enterobacterales*; CRAB: Carbapenem-resistant *Acinetobacter baumannii*; CRPA: Carbapenem Resistant *Pseudomonas aeruginosa*

Statistical analysis

All nominal data such as the type of antibiotics, indications, standard dose, standard frequencies, antibiotic combination, and length of therapy was analysed using chi square. All the parametric data in this study was tested with Kolmogorov-Smirnov test for normal distributions and found not normally distributed. The parametric data analysis was done by logistic regression method. Multivariate analysis of all the significant variables was done using logistic regression. The statistical analysis was done using Jamovi version 2.3.4.

RESULTS

A total of 304 Critical care patients with resistance detected from blood culture was found

Table 2. Demographic and critical care variables of the patients admitted in Critical Care Unit at Dr. Soetomo Academic General Hospital July 2023-June 2024

	DR (N = 172)	Non-DR (N = 183)	p-value	Odd Ratio (CI 95%)
Age (years)				
Median (min-max)	50 (19-76)	55 (20-89)	0.036	0.986 (0.972-0.999)
Gender[a]				
Male	93 (54.07%)	115 (62.84%)	0.094	0.696
Female	79 (45.93%)	68 (37.16%)		(0.456-1.06)
Critical care level[a]				
HCU	69 (40.12%)	82(45.05%)	0.799	0.825
ICU	103 (59.88%)	101 (55.95%)		(0.541-1.26)
Diabetes mellitus[a]				
Yes	30 (17.44%)	37 (20.22%)	0.504	0.834
No	142 (82.56%)	146 (79.78%)		(0.489-1.42)
CVA[a]				
Yes	40 (23.26%)	35 (19.13%)	0.341	1.28
No	132 (76.74%)	148 (80.87%)		(0.769-2.14)
Liver disease[a]				
Yes	2 (1.16%)	8 (4.37%)	0.106	3.89
No	170 (98.84%)	175 (95.63%)		(0.813-18.6)
Kidney disease[a]				
Yes	43 (25.0%)	80 (43.72%)	<0.001	2.33
No	129 (75.0%)	103 (56.28%)		(1.48-3.66)
Malignancy[a,b]				
Yes	15 (8.72%)	8 (4.37%)	0.096	2.09
No	157 (91.28%)	175 (95.63%)		(0.863-5.06)
Surgery[a]				
Yes	110 (63.95%)	103 (56.28%)	0.140	0.726
No	62 (36.05%)	80 (43.72%)		(0.474-1.11)
Burn[a]				
Yes	18 (10.46%)	0 (0%)	<0.001	43.9
No	154 (89.54%)	183 (100%)		(2.63-735)
Immune suppression medication[a,c]				
Yes	27 (15.70%)	14 (7.65%)	0.018	0.445
No	145 (84.30%)	169 (92.35%)		(0.225-0.88)
Device[a,d]				
CVC/Central line[e]	145 (84.30%)	161 (87.98%)	0.316	1.36 (0.743-3.5)
Endotracheal tube	107 (62.21%)	94 (51.37%)	0.039	0.642 (0.42-0.98)
Urinary catheter	168 (97.67%)	183 (100.0%)	0.054	9.8 (0.524-183)
Surgical drain[f]	28 (16.28%)	32 (17.49%)	0.762	1.09 (0.625-1.09)

DR: Drug-resistance group; Non-DR: Non-Drug-resistant group; CVA = Cerebrovascular accident; CVC = Central venous catheter [a]Number of prescriptions; [b]Malignancy found: metastatic carcinoma, leukaemia, and lymphoma; [c]Including glucocorticoid and immunoglobulin therapies; [d]Each patient may have more than 1 device; [e]Central venous catheter (CVC), Arterial lumen, and haemodialysis catheter included in this category; [f]Abdominal drain, chest tube, wound drain, and extra ventricular drain included in this category

Table 3. Antibiotic factors of the patients admitted in Critical Care Unit at Dr. Soetomo Academic General Hospital July 2023-June 2024

	DR[a] (N = 172)	%	Non-DR[a] (N = 183)	%	p-value	Odd Ratio	CI 95%
Type of antibiotic							
Ceftriaxone	36	20.93%	39	21.31%	0.93	0.977	0.587-1.63
Cefoperazone sulbactam	29	16.86%	44	24.04%	0.094	0.641	0.379-1.08
Metronidazole	25	14.53%	18	9.84%	0.175	1.56	0.818-2.97
Levofloxacin	19	11.05%	18	9.84%	0.709	1.14	0.576-2.25
Cefuroxime	13	7.56%	3	1.64%	0.009	4.91	1.37-17.50
Amikacin	8	4.65%	5	2.73%	0.336	1.74	0.557-5.42
Cefoperazone	7	4.07%	16	8.74%	0.074	0.443	0.178-1.1
Meropenem	6	3.49%	12	6.56%	0.188	0.515	0.136-0.917
Moxifloxacin	6	3.49%	17	9.29%	0.026	0.35	0.136-0.917
Cefazolin	5	2.91%	2	1.09%	0.271	2.71	0.519-14.2
Ampicillin sulbactam	2	1.16%	6	3.28%	0.285	0.347	0.069-1.74
Ceftazidime	2	1.16%	0	0.00%	0.234	5.38	0.257-113
Chloramphenicol	2	1.16%	0	0.00%	0.234	5.38	0.257-113
Gentamicin	2	1.16%	0	0.00%	0.234	5.38	0.257-113
Piperacillin tazobactam	2	1.16%	0	0.00%	0.234	5.38	0.257-113
Vancomycin	2	1.16%	0	0.00%	0.234	5.38	0.257-113
Cefepime	1	0.58%	1	0.55%	1	1.06	0.066-17.2
Cefotaxime	1	0.58%	0	0.00%	0.485	3.21	0.13-79.3
Ciprofloxacin	1	0.58%	0	0.00%	0.485	3.21	0.13-79.3
Cotrimoxazole	1	0.58%	1	0.55%	1	1.06	0.066-17.2
Linezolid	1	0.58%	0	0.00%	0.485	3.21	0.13-79.3
Tigecycline	1	0.58%	0	0.00%	0.485	3.21	0.13-79.3
Ampicillin	0	0.00%	1	0.55%	1	1.06	0.066-17.2
Indication							
Surgical prophylaxis	4	2.33%	1	0.55%	0.202	4.33	0.48-39.2
Non-Surgical Prophylaxis	24	13.95%	3	1.64%	<0.001	9.73	2.87-32.9
Empirical	98	56.98%	121	66.12%	0.077	0.679	0.441-1.04
Definitive	46	26.74%	58	31.69%	0.306	0.787	0.497-1.25
Dosing adjustment[b]							
Standard dose	135	78.49%	134	73.22%	0.247	1.33	0.818-2.18
Adjusted dose	37	21.51%	49	26.78%			
Frequency adjustment[b]							
Standard frequency	145	84.30%	133	78.69%	0.174	1.45	0.846-2.5
Adjusted frequency	27	15.70%	39	21.31%			
Combination therapy							
Monotherapy	91	52.91%	96	52.46%	0.933	0.982	0.647-1.49
2 antibiotics	78	45.35%	81	44.26%	0.837	0.957	0.63-1.45
3 antibiotics	3	1.74%	6	3.28%	0.504	1.91	0.47-7.76

DR: Drug-resistance group; Non-DR: Non-Drug-resistant group; [a]number of prescriptions; [b]standard and adjusted dose/frequency was based on Lexi-Drugs multinational antibiotic database, no irrational dosing was found during this study[29-51]

during the data collection, 207 patients were excluded and a total of 97 patients in the sample group. The same number of patients from critical care unit who had bloodstream infection but no resistance detected during hospitalisation period. A total of 172 antibiotic prescriptions were found in the sample group and 183 in the control group.

Majority of the bacteria found during this study were Gram-negative bacteria, both in the DR group (95.88%) and non-DR group (60.82%). *Escherichia coli* and *Klebsiella pneumoniae* were the dominant species in the DR group with 38.14% and 31.96% respectively. In the non-DR group, the most common species found during this study were *Staphylococcus aureus* (28.87%), followed by *Pseudomonas aeruginosa* (14.43%). The most common resistance found in this study is the and Extended-spectrum beta-lactamase producing *Enterobacterales* (56.7%) and extended drug-resistant microorganism (28.87%). Other types of

Table 4. Association between dosage, frequency, and duration of antibiotic exposure factors with the development of resistance in Critical Care Unit at Dr. Soetomo Academic General Hospital July 2023-June 2024

	DR (N = 172)	Non-DR (N = 183)	p-value	Odd Ratio	CI 95%
Dose	(mg/day)	(mg/day)			
Median Minimum-maximum	2000 (100-27000)	2000 (375-6000)	0.289	1	1.00-1.00
Frequency	(times/day)	(times/day)			
Median Minimum-maximum	2 (1-6)	2 (0.5-4)	0.013	1.327	1.063-1.658
Duration of exposure	(days)	(days)			
Median Minimum-maximum	6 (1-28)	5 (1-26)	0.607	0.988	0.943-1.03

DR: Drug-resistance group; Non-DR: Non-Drug-resistant group

Table 5. Total number antibiotics used and the length of antibiotic therapy for patients in Critical Care Unit at Dr. Soetomo Academic General Hospital July 2023-June 2024

Number of antibiotics	DR[a] (N = 97) (TOA/patient)		Non-DR[a] (N = 97) (TOA/patient)		p-value	Odd Ratio	CI 95%
Median Minimum-maximum	2 (0-5)		2 (0-6)		0.404	1.114	0.864-1.44
Length of therapy	(Number of patients)		(Number of patients)				
<=7 days	55	56.7%	59	60.83%			
8-14 days	18	18.56%	23	23.71%	0.796	0.995	0.961-1.03
>14 days	24	24.74%	15	15.46%			

DR: Drug-resistance group; Non-DR: Non-Drug-resistant group; TOA: Type of Antibiotic used
[a]The variables is counted for each patient (total 97 patients in DR group and 97 patients in non-DR group) from hospital admission until the resistance detected in blood culture (or the entire duration of hospitalization for non-DR group)

resistance were also found in lesser number like CRE (7.22%), MRSA (4.12%), CRAB (2.06%), and CRPA (1.03%).

The median age in the DR-group was 50 years old while non-DR group was 55 years old. The significant critical care factors found in this study were age ($p = 0.036$), kidney disease ($p < 0.001$), the use of immune suppression medication ($p = 0.018$), burn trauma ($p < 0.001$) and the use of Endotracheal tube (ETT) ($p = 0.039$). Kidney disease was found more prevalent in the non-DR group (43.72%) compared to the DR group (25.0%). The use of immune suppression medication was found more in the DR group (15.7%) compared to the non-DR group (7.65%). All of the burn patients in this study experienced bloodstream infection caused by drug-resistant bacteria. The use of ETT also found more often in the DR-group (62.21%). The detail of blood culture result in this study and the critical care variable can be found in Table 1 and Table 2.

Ceftriaxone usage was the highest in the DR-group is Ceftriaxone (20.93%) while Cefoperazone sulbactam is the most used antibiotic in the non-DR group (24.04%). Among the type of antibiotics we found that cefuroxime has higher risk of developing drug-resistance (OR = 4.91; CI 95% = 1.37-17.5; $p = 0.009$) while moxifloxacin has lower risk of resistance (OR = 0.35; CI 95% 0.136-0.917; $p = 0.026$). Most of the indication of antibiotic treatment in this study for empirical therapy either in DR-group (56.98%) and non-DR group (66.12%). However, we found non-surgical prophylaxis highly correlate with the development of drug resistance bacterial infection (OR = 9.73; CI 95% = 2.87-32.9; $p < 0.001$). The application of either adjusted dosage or frequency for patients with appropriate indications shows no significant correlation to the emergence of resistance, as all prescriptions utilizing adjusted dosage or frequency in this study were justified by valid reasons such as impaired renal function or

Table 6. Multivariate analysis of significant factor

Predictor	P	Odds ratio	95% Confidence Interval	
			Lower	Upper
Critical care variable				
Age	0.351	0.993	0.978	1.01
Immune suppression medication	0.008	2.709	1.30	5.65
Burn	0.975	$2.51x10^7$	0	Inf
Renal disease	0.484	0.829	0.489	1.40
Endotracheal tube	0.002	2.30	1.37	3.86
Type of antibiotic				
Cefuroxime	0.099	0138	0.013	1.45
Moxifloxacin	0.350	0.606	0.212	1.73
Indication				
Non-surgical prophylaxis	0.006	9.187	1.90	44.37
Antibiotic frequency	0.437	1.105	0.858	1.42

other conditions affecting drug pharmacokinetics. The same result was seen in the quantity of simultaneous antibiotic combinations where it did not show correlation to the development of antibiotic resistance. The complete details of the antibiotics factors can be seen in Table 3.

We analysed the dosing, frequency, and duration of exposure of each antibiotic to the development of resistance. The results were neither dosing nor duration of exposure had significant correlation with drug resistance in the bloodstream infection. However, our data showed that an antibiotic with higher frequency of administration per day might could increase the risk of resistance in bloodstream infection (OR = 1.327; CI 95% = 1.063-1.758; p = 0.013). The complete data of antibiotic dose, frequency, and duration of exposure affecting development of resistance can be seen in Table 4.

We also investigate the total number of antibiotics administered and the overall duration of antibiotic treatment for each patient. Both the total number of antibiotics and the total duration of therapy did not significantly influence the emergence of resistance in this investigation. The analysis of the total number of antibiotics administered and the overall duration of therapy can be seen in Table 5.

To validate or refute prior findings, simple regression analysis was used to compare the two groups. The variables with $p < 0.05$ in the bivariate analysis were included in the multivariate analysis. The result of the multivariate analysis shows that non-surgical prophylaxis uses could significantly increase the risk of the development of resistance in bloodstream infection (adjusted OR = 9.187; CI 95% = 1.9-44.37; p = 0.006). Other variables that had significant effect such as the use of endotracheal tube (adjusted OR = 2.30; CI 95% = 1.37-3.86; p = 0.002) and immune suppression medication (adjusted OR = 2.709; CI 95% = 1.3-5.65; p = 0.008). The multivariate analysis can be seen in Table 6.

DISCUSSION

This study found no significant correlation between the type of antibiotic administered and the occurrence of resistance. In a study in Saudi Arabia in 2023, cefazolin, imipenem, amikacin, and cotrimoxazole could increase the risk of developing resistance.[6] In a systematic review in China, carbapenem and cephalosporin were found to increase the risk of antibiotic resistance.[12] The disparity in results may be attributed to variations in antibiotic resistance trends, as cefazolin, imipenem, amikacin, and cotrimoxazole were infrequently prescribed at Dr. Soetomo Academic General Hospital during the study period.[6] Ceftriaxone was the first empirical therapy choice for systemic infection in critical condition with normal renal function in Dr. Soetomo Academic General Hospital with cefotaxime as its alternative and since empirical usage is the dominant antibiotic

indication in this study, ceftriaxone was the most used antibiotics.[13,14] Metronidazole was used for suspected anaerobic infection and commonly used in combination with ceftriaxone for suspected infection that originated from intraabdominal source or complicated skin infection such as necrotizing fasciitis.[13,14] Ceftazidime was the first choice for suspected *Pseudomonas* species infection, while Cefoperazone-sulbactam used as alternative for severe cases since the local data in Dr. Soetomo Academic General hospital showed good susceptibility for it.[13,14] For patients with impaired renal function where sulbactam was avoided, cefoperazone was used. Fluoroquinolone such as levofloxacin and moxifloxacin were an alternative for infection which suspected originated from respiratory tract or some condition where ceftriaxone usage did not show any improvement.[13,14,42] Cefazolin was limited to be used only as surgical prophylaxis, with ceftriaxone can be used as alternative if cefazolin wasn't available.[13,14] Ampicillin sulbactam single drug was the first choice for urosepsis empirical therapy accordance to local data.[13] Ampicillin sulbactam in combination with gentamicin was commonly used for alternative in intraabdominal infection.[13] Other antibiotics like Vancomycin, Amikacin, Meropenem, Tigecycline, Linezolid, and Cotrimoxazole injection were kept as reserve antibiotics and only used as definitive therapy with prior antibiotic susceptibility result.[13,14] However, in certain cases, these antibiotics may be used as empirical therapy, for example, Vancomycin is allowed to be used in a suspected MRSA infection.[13]

There was also difference in the species of the bacteria found from the culture where as in China the dominant species were *Klebsiella pneumoniae* (38.6%) and *Pseudomonas aeruginosa* (34.1%), in Saudi Arabia *Klebsiella pneumoniae* (21.5%) and *Staphylococcus aureus* (14.8%), while in this study are *Escherichia coli* (24.7%) and *Klebsiella pneumoniae* (19.6%).[6,12] The dominant type of resistance also might play a role in this difference since the most common resistance type found in this study is ESBL-E which is similar to previous study in Indonesia while carbapenem resistant more often found in the study in Saudi Arabia.

There was no association between antibiotic dose or frequency with the onset of resistance. In drug administration, particularly antibiotics, alterations in the patient's metabolic and excretion parameters typically necessitate dose modifications to mitigate toxicity and optimize circulating drug concentration.[11] A systematic study in 2021 revealed that patients with renal impairment receiving a modified dose of meropenem exhibited blood levels of the drug ranging from 158% to 286% of the normal dose observed in individuals without renal impairment.[43] A separate investigation into time-dependent antibiotics, specifically beta-lactams, revealed that the duration for which the concentration of beta-lactam antibiotics exceeded the MIC (fT > MIC) did not significantly correlate with the emergence of resistance; however, a ƒAUC/MIC greater than 494 could diminish the likelihood of resistance.[44] This prove that adjusted regiment is no inferior than standard regiment in the correct situation, and during this study all the antibiotic dosing and frequencies was in accordance to the guideline used in Dr Soetomo Academic Hospital.[15-37]

Based on the 2022, the number of antibiotic prescriptions $\geq$3 may increase the likelihood of resistance through prescribing errors due to human error.[8] Since most of the antibiotic combination found in this study <3 (DR group: 98.26%, non-DR group: 96.72%), there is no significant correlation between the antibiotic combination and antimicrobial resistance.

The duration of antibiotic exposure in this study did not have a significant relationship. In another study conducted to see the increase in beta-lactam MIC on Gram-negative bacteria, the first 7 days of exposure did not show a significant effect on the increase in MIC.[44] In another study observing the effect of antibiotic exposure to *Staphylococcus aureus*, an increase in MIC was observed on day 8.[45] In this study, most of the antibiotics were prescribed $\leq$7 days (DR group: 65.70%; non-DR group: 69.95%), hence the bacteria did not have enough time to develop resistance. As for the total number and duration of therapy, since both DR and non-DR group using the same guideline for treatment, no significant difference between the two group and the bacterial resistance in bloodstream infection.[14,46]

The use of antibiotic prophylaxis inherently carries a risk of exacerbating bacterial resistance; but, under some circumstances, prophylactic medication may effectively prevent infections and enhance patient outcomes.[38-40,47] The most well-defined antimicrobial prophylaxis use is the surgical prophylaxis which is given 30-60 minutes before surgery for up to 24 hours (may extend to 48 hours following cardiothoracic surgery) and proven can reduce rate of surgical site infection by 80%.[39] Empirical and definitive therapy is given to treat the infection that already happen for patients with the high likelihood of infection, or the outcome is likely to be affected adversely by delayed therapy, it is appropriate and prudent for hospitals to develop systems in which patients are expeditiously recognized and promptly treated with an antimicrobial regimen that is broad enough to cover all plausibly likely pathogens.[48]

This study revealed that non-surgical prophylaxis significantly elevates the likelihood of antibiotic resistance in bloodstream infections (adjusted OR = 9.187; CI 95% = 1.9-44.37; p = 0.006). In total, there were 32 antibiotics prescribed as prophylaxis, and 27 of them were prophylaxis in non-surgical cases. We analysed 27 non-surgical prophylaxis treatment prescribed in this study and found: 14 (51.85%) of them were prophylaxis in high grade burn patients, 8 (29.63%) in immunocompromised patients either due to cancer or blood disorders, 5 (18.52%) in trauma patients with open wound.

There were 18 burn patients found in this study, and all of them fulfil the criteria of burn patient's referral in accordance to The American Burn Association recommendation by being partial thickness burn >10% total body surface area.[49] In burn patient, there were changes in pharmacokinetics since there will be an increase of renal blood flow and loss of albumin through the wound resulting in increased elimination and alteration of drug concentration caused by the loss of albumin.[50] Cefuroxime, a second-generation cephalosporin, was the drug of choice for prophylactic antibiotic for burn patients in Dr. Soetomo Academic Hospital since it has relatively good effectiveness, much cheaper and low protein binding (16-33%).[51,52] However, the alteration of pharmacokinetics in burn patients varies from case to case therefore individualized dose adjustment is needed.[50] In 2010, a systematic review found that the use of prophylactic antibiotic in burn patients may reduce 50% in all cause of mortality.[53] However, in other research in 2020, antibiotic usage is not recommended in all grade burn patients unless they have pneumonia or inhalation injury.[41] The burn patients which categorized in the non-surgical prophylaxis has neither sign of pneumonia or inhalation injury and none of the antibiotics prescribed has their dose adjusted. These could be the reasons why the resistance occur, however only small number of burn patients found in this study to reach that conclusion.

The usage of prophylactic antibiotic in the immune compromised group is not contraindicated, but must be reserved for those who have high risk of infection i.e. absolute neutrophil count ≤100 cells/mm^3 for >7 days.[47] In this non-surgical prophylaxis group, the immune suppressed patients were those who have malignancy since no HIV, diabetes mellitus or other type of immune suppression found in this specific category. Only 2 out of 8 prescription is given in the high-risk situation, and 7 out of 8 developed bacterial resistance in the bloodstream infection. For the open wound trauma, in fact antibiotic prophylaxis is highly recommended, however prolonged administration (7-10 days) did not have much benefit for the infection prevention.[40] In our study, 3 of the prescription were given >7 days and resistance developed for all the patients, while the other 2 which prescribed for <7 days, only 1 of them developed resistance.

Other factors found significant in this study is the use of endotracheal tube (ETT) and immune suppression medication. ETT in the trachea disrupts the natural defence mechanism of physiological mucus clearance and results in the formation of biofilm and mucus on the intraluminal surface of the ETT.[54] Both suctioning and the inspiratory flow through the ETT may create enough shear force to detach biofilm fragments and reach the lower respiratory tract.[54] Infections involving a biofilm component are often chronic and highly recalcitrant to antibiotic therapy because of intrinsic physical factors including extracellular matrix production, low growth rates, altered antibiotic target production and efficient exchange of resistance genes.[55] In

this study, it was found that 68.22% of the patient with drug-resistant bloodstream infection which was intubated also experienced pneumonia and bloodstream infection possibly resulted secondary from the respiratory tract infection.[56]

Previous studies states that the dysfunctional immune system poses challenges to the effectiveness of antibiotic therapy, increasing the likelihood of treatment failure since antibiotics cooperate with host responses to clear infections and antibiotic failure would increase the incidence of resistance.[57] The state of immunosuppression may vary from primary immunodeficiency that is caused by genetic disorder or secondary which was acquired such as diabetes mellitus, cancer, AIDS, autoimmune disease, malnutrition, geriatric, or intervention such as surgeries and immune suppression medication.[57] In type 2 diabetes mellitus for example, there were alteration in absorption due to decrease of 60-70% mucosal blood flow.[58] Even if bypassing the first pass effect in patients with diabetes mellitus, high blood glucose will cause glycosylation of albumin resulting in increase of unbound antibiotic which in return increase the clearance of antibiotic leading to suboptimal concentration in plasma.[58] As discussed before, in burn patient, there was an increase of renal blood flow and loss of albumin through the wound resulting in increased elimination and alteration of drug concentration caused by the loss of albumin.[50] Other immunosuppression state could cause chemotactic and phagocytic defects in neutrophils, and lymphocyte dysfunction, significantly increase the host's susceptibility to certain infections and reduce the effectiveness of antibiotic treatment.[57] There were no AIDS patient found during the data collection. In this study, all the patients were critically ill but no significant correlation found between comorbidities that could suppress immune system like old age, diabetes mellitus, malignancy, liver disease, kidney disease, surgery, or major burn.

However, the continuous use of immune suppression medication correlates strongly to the development of resistance ($p = 0.008$; adjusted OR 2.709; CI 95%: 1.30-5.65). Among those who used immune suppression medication, 2 patients from the drug-resistant group and 1 patient from control group used IVIG due to Guillain-Barr' syndrome. One patient from the drug-resistant group were a Systemic Lupus Erythematosus patient that use long term methylprednisolone. No other autoimmune disease was found, and the other patients were given corticosteroid treatment in form of continuous pump of methylprednisolone or prednisone to alleviate their inflammation for more than 5 days. Corticosteroids produce their effect through multiple pathways, the glucocorticoid receptor is located intracellularly within the cytoplasm and, upon binding, translocates rapidly into the nucleus, where it affects gene transcription and causes inhibition of gene expression and translation for inflammatory leukocytes leads to a reduction in proinflammatory cytokines, chemokines, cell adhesion molecules, and other enzymes involved in the inflammatory response.[59] The resistance found in the drug-resistant group were ESBL (80.0%), CRE (13.33%), and XDR (6.67%). The duration between hospital administration and the development of resistance among the immunosuppressant users varied from 3 days to 41 days (mean 12.5 days) so it is unclear if it will hasten bacterial resistance. The length of stay in the immune suppression medication group averaged 24.6 days (varied from 5-53 days) and 15.8 days (varied from 4-69 days) for those who didn't get the medication while the mortality rate does not show significant difference being 22.72% (5 death in 22 patients) for the those who get the immune suppressant and 25.58% (44 death in 172 patients) for those who are not ($p = 0.772$) but it might be bias due to unbalanced amount between the group. The effect of phospholipase A2 inhibition, which is critical for producing inflammatory cytokines, impairing release of arachidonic acid, regulation of apoptosis in thymocytes and inhibition of B cells and T cells production caused by steroid therapy would render the host susceptible to infection.[59] A glucocorticoid such as dexamethasone was reported having the capability to induce CYP3A4 and CYP2C9 which would alter the concentration antibiotics that metabolized by them.[60] Another report showed that hormonal steroid therapy may induce drug resistant by increasing the expression of multidrug efflux pump operon *mtrCDE* through inhibition of regulator MtrR.[61] Further research might be needed to conclude whether continuous immunosuppressant medication really promote

the development of resistance different from other states of immune suppression especially the expression of ESBL in *Enterobacterales*.

This study has limitations, notably that the evaluation of blood cultures was conducted irregularly, contingent upon alterations in the patient's state, making it challenging to determine the onset of infection by drug-resistant bacteria. This study exclusively assessed bloodstream infections, thereby precluding the evaluation of bacterial resistance development at the local wound or organ site. This study was conducted at a single hospital in Indonesia; hence it scarcely represents the broader community situation. The variability in the quantity of resistances present complicates the analysis of each resistance type. This study did not analyse additional characteristics such as visitor count, infection control protocols, and caregiver involvement. Comprehensive research on a wider scale is required to substantiate the danger associated with antibiotic administration and other factors concerning the occurrence of bacterial resistance, particularly in specific populations such as burn victims, immunocompromised individuals, or trauma patients.

CONCLUSION

Our study indicates that in adult population with critical illness in Dr. Soetomo Academic Hospital, among all the factors that involve antimicrobial therapy, prophylactic use in non-surgical contexts increase the rate of resistance more significantly than other factors such as type of antibiotics, adjustment dose, duration of exposure, or number of combination therapy. The use of mechanical ventilation could also increase the rate of bacterial resistance from biofilm and bacterial translocation to bloodstream in critical care settings. This study also found that in critical patients, the immune suppression caused by medication like corticosteroids may correlate with the increase of bacterial resistance in bloodstream infection compared to other state of immune suppression. However, to validate these findings in larger population, further research on wider scale is necessary.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Ethical Committee of the Dr. Soetomo Academic General Hospital (No. 1643/LOE/301.4.2/IV/2024).

INFORMED CONSENT

Written informed consent was obtained from the participant before enrolling in the study.

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