Brief Original Article | Iran J Med Microbiol. 2023; 17(5): 596-605

10.30699/ijmm.17.5.596

Iranian Journal of Medical Microbiology | ISSN:2345-4342

Multidrug-Resistant Organisms and Determinant Factors in Sepsis Patients

Fadrian Fadrian[1,2*], Linosefa Linosefa[3,4], Muhammad Ridhwan F[5], Hidayatul Hasnah[6], Alya Syafa Ayuni[6]

1. *Division of Tropical and Infectious Disease, Department of Internal Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia*
2. *Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia*
3. *Department of Clinical Microbiology, Dr. M. Djamil General Hospital, Padang, Indonesia*
4. *Department of Clinical Microbiology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia*
5. *Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia*
6. *Faculty of Medicine, Universitas Andalas, Padang, Indonesia*

ABSTRACT

Background and Aim: Antibiotic resistance has a major contribution to human health. As reported in 2009, Indonesia ranked 8th out of 27 countries with the highest MDRO rate in the world. To determine the risk factors of infection due to MDROs at Dr.M.Djamil General Hospital in sepsis patients, it is necessary to identify the factors that cause MDROs; thus, effective prevention and control methods can be planned.

Materials and Methods: This was a cross-sectional study conducted on 101 patients with 124 isolates diagnosed with sepsis who were treated at Dr.M.Djamil General Hospital. The characteristics and factors associated with MDROs in sepsis patients were recorded for each subject. Then, a bacterial culture examination was performed with blood culture and other cultures depending on the focus of infection. A descriptive analysis was conducted to analyze the frequency distribution of each research variable. Bivariate analysis was performed to determine the relationship between each variable and infection due to MDROs in sepsis patients, and multivariate logistic regression analysis was performed to find the most dominant variable.

Results & Conclusion: History of antibiotic use (P<0.05) and urinary catheter use (P<0.05) had a significant correlation with infection due to MDROs, and urinary catheter use and history of antibiotic use were the strongest risk factors associated with infection due to MDROs in sepsis patients admitted to Dr.M.Djamil General Hospital. Antibiotics should be used wisely and rationally in managing infectious patients, and the use of urinary catheters should be done more selectively for inpatients to prevent the development of MDROs as a cause of infection.

Keywords: Antibiotics, Hospital, MDROs, Sepsis

Received: 2023/07/18; **Accepted**: 2023/10/21; **Published Online:** 2023/11/29

Corresponding Information: **Fadrian**, *Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia* Email: fadrian@med.unand.ac.id

Use a device to scan and read the article online

Fadrian F, Linosefa L, Ridhwan F. M, Hasnah H, Syafa Ayuni A. Multidrug-Resistant Organisms and Determinant Factors in Sepsis Patients. Iran. Iran J Med Microbiol. 2023;17(5):596-605.

Download citation: BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks

Send citation to: Mendeley Zotero RefWorks

1. Introduction

Antibiotic resistance has the greatest impact on human health, at least 2 million people are infected by antibiotic-resistant bacteria and at least 23.000 people die each year as a direct result of these infections. According to data in 2009, Indonesia ranked 8th out of 27 countries with the highest multidrug-resistant rate in the world. A study conducted at the National General Hospital Dr. Cipto Mangunkusumo, University of Indonesia in 2021 found that the prevalence of community-acquired

pneumonia caused by drug-resistant pathogens was 40.6% with 52 isolates of gram-positive bacteria and 271 isolates of gram-negative bacteria **(1-3)**.

Multidrug-resistant (MDR) is a condition in which bacteria are resistant to at least one type of antibiotic from ≥3 classes of antibiotics. Several things, including the inappropriate use of antibiotic doses, missed diagnostics, and incorrect causative bacteria can cause MDR. Multidrug-resistant organisms (MDROs) are microorganisms, especially bacteria that are MDR. Some MDROs are *Methicillin-resistant Staphylococcus aureus* (MRSA), *Vancomycin-resistance Enterococcus* (VRE), *Extended-Spectrum Beta-Lactamase* producers (ESBLs), *Acinetobacter baumannii*, *Clostridium difficile*, and *Klebsiella pneumoniae* **(4, 5)**.

The Center for Disease Dynamics, Economics and Policy (CDDEP) reported in the "World Antibiotic Country Report 2015" that the incidence of infections from MDROs, such as MRSA, is rapidly increasing worldwide. The burden of antimicrobial resistance in low-income countries is several times higher than in high-income countries. While there is significant research on antibiotic resistance and the impact of MDROs in high-income countries, research on the causes, determinants, and solutions to MDROs in low- and middle-income countries, such as India, is limited **(6)**.

Understanding the pathogenesis and risk factors for the occurrence of infections due to MDROs is important to plan specific strategies for prevention. The survival and composition of the bacterial community depend on many factors, including perinatal factors, dietary, age, gender, and antibiotic exposure **(7-9)**. Other risk factors for MDROs include the elderly population, comorbid diseases, the severity of illness, hospital exposure or previous treatment history, immunosuppressive conditions and/or therapy, nutritional factors, history of antibiotic use, and medical device use such as endotracheal tubes, urinary catheters, and nasogastric tubes **(10, 11)**.

Sepsis is defined as life-threatening organ dysfunction due to dysregulation of the body's response to infection. The World Health Organization has recently recognized it as a global health priority. According to the SSC guideline, broad-spectrum antibiotics within the first hour are recommended in patients with sepsis and septic shock. However, inappropriate antibiotic administration will increase antibiotic resistance. In addition, clinicians should also consider the possibility of MDROs in sepsis patients **(12)**.

To determine the risk factors of MDROs infection in Dr. M. Djamil General Hospital in sepsis patients, as mentioned above, it is necessary to identify the most frequent factors that cause MDROs; thus, effective prevention and control methods can be planned. MDROs themselves will increase the burden of expenses and also the use of third-line antibiotics and increase mortality if not treated properly.

2. Materials and Methods

This study was done using a cross-sectional method conducted at Dr. M. Djamil General Hospital starting in August 2022. The population of this study was all patients with a diagnosis of sepsis who were admitted to the ward of the Department of Internal Medicine and other wards treated together with the Division of Tropical and Infectious Diseases of Dr. M. Djamil General Hospital. The samples of this study were subjects from the study population who met the inclusion criteria (age > 18 years, agreed as research subject) and did not have exclusion criteria (refused to be the subject of the study, patients with no microorganisms growth in the culture results).

We collected data such as age, gender, comorbidity, and severity of illness assessed based on SOFA score, nutritional factors as seen from Body Mass Index (BMI), history of antibiotic use, and medical device use. Then a bacterial culture test is performed with blood culture in addition to the other cultures (sputum, urine, feces, or pus) depending on the focus of infection. All culture specimens were sent to the Microbiology Laboratory of Dr. M. Djamil General Hospital.

The analysis of this study included descriptive, bivariate, and multivariate analysis. Descriptive analysis was performed to see the frequency distribution of each variable. Numerical data were presented in the form of numbers and percentages. Bivariate analysis determined the relationship between each variable and the number of MDROs in sepsis patients. Bivariate analysis was performed using the chi-square test. If P-value< 0.05, it was considered significant. If the P-value was < 0.25, then the variable would be included in the multivariate analysis. Multivariate analysis began with a logistic regression test to identify indicators that were risk factors for mortality. If it is known that the P-value< 0.05 and the prevalence odd ratio (POR) with the most value > 1, it is considered the most dominant factor.

3. Results & Discussion

In this study, we analyzed the factors associated with the incidence of MDROs in sepsis patients admitted to Dr. M. Djamil General Hospital, including gender, age, comorbidity, SOFA score, infectious disease, history of antibiotic use, nutritional status (BMI), medical device use, type of bacteria causing

sepsis, antibiotic escalation, and initial empirical antibiotic administration in 101 patients consisting of 124 isolates with 83 MDROs isolates.

There were 101 patients with 124 isolates that met the inclusion and exclusion criteria of the study, consisting of 64 patients with 83 (66.93%) MDRO isolates and 37 patients with 41 (33.06%) non-MDRO isolates. Among the 83 MDRO isolates, we found 54 (65.06%) ESBL isolates, 15 (18.07%) CRO isolates, 13 (15.66%) MRSA isolates, and 2 (2.40%) VRE isolates. Characteristics of the study subjects are shown in Table 1.

Table 1. Characteristics of the study subjects

Characteristics	MDROs n=83 (%)
Age	
18-65 years	52(62.7%)
> 65 years	31(37.3%)
Gender	
Male	48 (57.8%)
Female	35 (42.2%)
Severity Of Illness (SOFA Score)	
1-6	35 (42.2%)
7-12	38(45.8%)
13-18	9(10.8%)
19-24	1 (1.2%)
Body Mass Index	
Normal	44 (53%)
Underweight	24(28.9%)
Overweight-Obese	15(18.1%)
History of antibiotic use	
Yes	61 (73.5%)
No	22 (26.5%)
Medical devices	
Urine catheter	76 (91.6%)
Nasogastric tube	70 (84.3%)
Endotracheal tube	4 (4.8%)
Mortality in 14 days	
Yes	51 (61.4%)
No	32 (38.6%)
Initial empirical antibiotics	
Cefepime + Levofloxacin	37 (44.6%)
Ceftriaxone + Levofloxacin	7 (8.4%)
Ceftriaxone	6 (7.2%)
Meropenem + Levofloxacin	4 (4.8%)
Ciprofloxacin	4 (4.8%)
Meropenem + Vancomycin + Metronidazole	3 (3.6%)
Ceftriaxone + Azithromycin	3 (3.6%)
Ceftriaxone + Levofloxacin + Metronidazole	3 (3.6%)
Cefotaxime + Ciprofloxacin	2 (2.4%)

Characteristics	MDROs n=83 (%)
Cefoperazone sulbactam + Amikacin	2 (2.4%)
Meropenem + Amikacin	2 (2.4%)
Cefoperazone	2 (2.4%)
Ampicillin sulbactam + Levofloxacin	2 (2.4%)
Meropenem	1(1.2%)
Ceftazidime + Levofloxacin	1(1.2%)
Ceftazidime	1(1.2%)
Cefepime + Levofloxacin + Metronidazole	1(1.2%)
Ceftriaxone + Metronidazole	1(1.2%)
Moxifloxacin + Metronidazole	1(1.2%)
Cefoperazone + Levofloxacin	1(1.2%)
Diagnosis of infectious disease	
Hospital-acquired pneumonia	45 (54.2%)
Community-acquired pneumonia	21 (25.3%)
Urinary tract infection	8 (9.6%)
Skin and soft tissue infections	5 (6.0%)
Gastrointestinal infection	3 (1.2%)
Intra abdominal infection	1 (3.6%)
Empirical Antibiotic Escalation	
Yes	27 (32.5%)
No	56 (67.5%)
Type of bacteria	
Klebsiella pneumoniae	23 (27.7%)
Escherichia coli	22 (26.5%)
Staphylococcus aureus	13 (15.7%)
Acinetoobacter baumannii	11 (13.3%)
Enterobacter cloacae	6 (7.2 %)
Enterococcus faecalis	2 (2.4%)
Staphylococcus haemolyticus	1 (1.2%)
Pseudomonas aeruginosa	1(1.2%)
Raoultella planticola	1(1.2%)
Moraxella sp	1(1.2%)
Enterococcus aerogenes	1(1.2%)
Stenotrophomonas maltophilia	1(1.2%)

Most subjects were males with MDRO criteria (57.8%) compared to non-MDRO criteria (51.2%). There were also more MDRO criteria found in women (42.2%). The results of this study are in line with research conducted at the Arifin Achmad Regional General Hospital, Riau Province, in 2017, which shows the characteristics of research subjects with sepsis tend to be more common in males (51.85%). Theoretically, this is due to the effect of the 5a-dihydrotestosterone (DHT) hormone, which can suppress the number of anti-inflammatory cytokines that impact the growth of bacteria. Whereas in women, the estrogen hormone has an immunoprotective effect on immune function **(13)**.

Another factor is age, which in this study was more prevalent in subjects aged 18-65 years with MDRO criteria (62.7%). This study categorized age into two groups, 18-65 years old and > 65 years old, because, at an older age, the immune system has decreased; thus, they are more susceptible to sepsis. This is consistent with research conducted at the Arifin Achmad Regional General Hospital in Riau Province in 2017 on sepsis patients in the age group of 17-65 years (74.04%) **(13)**.

Table 2. The Comorbidities of The Study Subjects

Comorbid Disease	MDROs n=89 (%)
Comorbidity	
Chronic kidney disease	25 (28%)
Type 2 Diabetes Mellitus	17 (19.2%)
Malignancy	11 (12.4%)
Stroke	9 (10.2%)
Hypertension	8 (8.9%)
Heart failure	8 (8.9%)
Chronic liver disease	5 (5.7%)
Chronic lung disease	4 (4.5%)
Autoimmune disease	1 (1.1%)
Human Immunodeficiency Virus	1 (1.1%)

Comorbid diseases are also one of the factors reviewed in this study as a risk factor for MDROs. In 64 sepsis patients with MDROs isolated, several patients had more than 1 comorbid disease (Table 2). There were 89 comorbid diseases in this study, with the highest number of comorbidities being chronic kidney disease, type 2 diabetes mellitus, and malignancy. A study at Dr. Moewardi Surakarta Regional General Hospital in 2021 which observed the correlation between antibiotic resistance and the incidence of sepsis and hospital mortality in the population with bacterial pneumonia infection, showed that the participants had several comorbid diseases in patients with MDROSs with the majority were cerebrovascular disease (15.8%), uncomplicated diabetes mellitus (13.2%), and chronic kidney disease (10.5%) **(14)**. Zilberberg et al. in 2014 showed different results; out of 311 sepsis patients who died, 41.16% had malignancy as a comorbid disease, 29.58% had COPD, and 25.40% had diabetes **(15)**.

Body Mass Index (BMI) in assessing the nutritional status of sepsis patients in this study was 53.0% in normal BMI status with the MDROs category, 28.9% were underweight, and 18.1% were overweight-obese with the MDROs category. This result shows that most of the subjects have a normal BMI (53.0%). This is similar to a study in the Department of Microbiology, Magdeburg, Germany, in 2021, which showed that most sepsis patients had a normal BMI (64.1%) **(16)**.

The antibiotic use as initial therapy for sepsis patients with MDROs used a combination of therapeutic regimens such as Cefepime + Levofloxacin (44.6%), Ceftriaxone + Levofloxacin (8.4%), and Meropenem + Levofloxacin (4.8%), in addition, single empirical therapy was also given to the subjects such as the use of Ceftriaxone (7.2%) and Ciprofloxacin (4.8%). A review article by Martinez et al. in 2019 explained that the use of combination therapy using two different classes of antibiotics is useful for accelerating pathogen clearance and ensuring pathogen susceptibility to treatment. However, monotherapy is usually used to reduce antibiotic pressure, i.e., the incidence of superinfections or the emergence of new infections. Studies on the efficacy of combination therapy have shown mixed results, with some observational studies showing the superiority of combination therapy over monotherapy in patients with sepsis and septic shock **(17)**.

In this study, the most common infectious disease causing sepsis was Hospital Acquired Pneumonia (54.2%) followed by Community Acquired Pneumonia (25.3%). Hospital-acquired Acquired Pneumonia is diagnosed when pneumonia occurs after the patient has been hospitalized for more than 48 hours, while Community-Acquired Pneumonia is diagnosed when pneumonia is acquired without a previous history of hospitalization.

In sepsis patients with MDRO infection, empirical antibiotics with a broad spectrum are needed. In this study, sepsis patients with MDROs received antibiotic escalation by 32.5%. This may be due to the initial empirical antibiotic selection in this study that was well enough, thus we did not perform antibiotic escalation in patient care.

In this study, at least 73.5% of subjects with MDROs had a history of antibiotic use. This is consistent with Nicolo et al. 's study in Milan, Italy, from 2011 to 2015, which showed that 76.6% of sepsis patients had at least one risk factor for MDROs, one of which was a history of antibiotic therapy in the last 90 days **(11)**.

Various bacteria caused MDROs in our subjects; the most common bacteria found were *K. pneumonia* (27.7%), *Escherichia coli* (26.5%), *Staphylococcus aureus* (15.7%), followed by *A. baumannii* (13.3%). In line with a study in the GICU of DR. Mohammad Hoesin Palembang Central General Hospital in 2018, the results of bacterial culture showed that the three most common types of bacteria were *A. baumannii* (33%), *Pseudomonas aeruginosa* (24%), and *K. pneumoniae* (11%) **(18)**.

In this study, the most common type of MDROs was ESBL (43.5%), followed by CRO (12.1%), with the most

types of specimens found to be sputum specimens, with 63 specimens out of a total of 83 MDROs specimens (Table 3).

Table 3. MDROs type based on culture specimen

MDROs type	Specimen					Total
	Sputum	Urine	Blood	Pus	Feces	
ESBL	29 (46.0%)	12 (60.0%)	5 (19.2%)	5 (41.7%)	3 (100%)	54 (43.5%)
CRO	11 (17.4%)	1 (5.0%)	2 (7.6%)	1 (8.3%)	0 (0.0%)	15 (12.1%)
MRSA	4 (6.3%)	0 (0.0%)	8 (30.8%)	1 (8.3%)	0 (0.0%)	13 (10.5%)
VRE	0 (0.0%)	1 (5.0%)	0 (0%)	1 (8.3%)	0 (0.0%)	2 (1.6%)
Non MDROs	19 (30.2%)	6 (30.0%)	11 (42.3%)	4 (33.3%)	0 (0.0%)	41 (32.3%)
Total	63 (100%)	20 (100%)	26 (100%)	12 (100%)	3 (100%)	124 (100%)

Abbreviation: MDROs = multidrug-resistant microorganisms, ESBL = extended-spectrum beta-lactamase producing enterobacteria, CRO = carbapenem resistance organisms, MRSA = methicillin-resistant staphylococcus aureus, VRE = vancomycin resistance enterococcus

In this study, it was found that the most types of MDROs were ESBL types (43.5%), followed by CRO (12.1%), with the majority of specimens coming from sputum specimens in a total of 63 sputum specimens, 26 blood specimens, 20 urine specimens, 12 pus specimens, and 3 feces specimens. A total of 124 isolates were obtained from 101 patients. Out of 101 patients, 64 patients resulted in 83 MDROs isolates. A study in Nanjing Hospital, China, 2020 on MDRO patients found that CRAB was the most common type of MDRO (820), followed by CRE (710), MRSA (413), and CRPA (371). Meanwhile, the specimens with the most MDROs were BALF (9.75%) and sputum (3.07%). Generally, specimens used to examine lower respiratory tract infections are sputum and BALF. Still, sputum tends to be easily contaminated by oral colonizing bacteria compared to BALF specimens which are alveolar surface fluid collected by bronchoscopy with less possibility of contamination and has sensitivity and specificity in the diagnosis of lower respiratory tract infections **(19)**.

Table 4 showed that there was a statistically significant correlation (p = 0.024) between the history of antibiotic use and the incidence of MDROs. The use of urinary catheters also had a statistically significant association (*P*=0.031) with infection due to MDROs in this study. There was no statistically significant association between other variables and the incidence of MDROs in this study.

Table 4. Characteristics of sepsis patients with MDROs and non-MDRO culture results

Characteristics	MDROs criteria		*P*
	MDROs n=83 (%)	Non MDROs n=41(%)	
Age			1.000
18-65 years	52 (62.7)	26 (63.4)	
>65 years	31 (37.3)	15 (36.6)	
Gender			0.614
Male	48 (57.8)	21 (51.2)	
Female	35 (42.2)	20 (48.8)	
Severity Of Illness (SOFA Score)			0.932
1-6	35 (42.2)	18 (43.9)	
7-12	38 (45.8)	17 (41.5)	

Characteristics	MDROs criteria		*P*
	MDROs n=83 (%)	Non MDROs n=41(%)	
13-18	9 (10.8)	5 (12.2)	
19-24	1 (1.2)	1 (2.4)	
Body mass index			0.633
Normal	44 (53.0)	18 (43.9)	
Underweight	24 (28.9)	14 (34.1)	
Overweight-Obese	15 (18.1)	9 (22.0)	
History of antibiotic use			0.024*
Yes	61 (73.5)	20 (48.8)	
No	22 (26.5)	21 (51.2)	
Medical Devices			
Urine catheter	76 (91.6)	31 (75.6)	0.031*
Nasogastric tube	70 (84.3)	30 (73.2)	0.215
Endotracheal tube	4 (4.8)	0 (0.0)	0.374
Thorax tube	0 (0.0)	1 (2.4)	0.713

*Significant risk factor at p<0.05

A statistically significant association was found (*P*= 0.024) in this study which assessed the association between the history of antibiotic use and the incidence of MDROs. A Korean study using data from 2004, 2008, and 2012 by Bongyoung et al. demonstrated the presence of microbial resistance due to an increased history of antibiotic use. An increase in *A. baumannii* resistance to imipenem (*P*=<0.001) correlated with increased carbapenem use, as well as *E. coli* or *K. pneumoniae* resistance to ciprofloxacin (*P*=0.001) correlated with carbapenem use. This supports the idea that increasing antibiotic resistance is caused by the increasing use of broad-spectrum antibiotics and antibiotics against MDR pathogens **(20)**. In addition, the development of bacterial resistance to antibiotics is affected by the rapid evolution of the bacterial genome under selective antibiotic pressure and by selective pressure from the environment. Selective pressure from the continuous and routine use of antibiotics is the initial condition for increasing multi-resistant strains **(21)**.

The use of urinary catheters significantly correlates (*P*=0.031) with infection due to MDROs in this study. A 2015 study by Nicolo et al. in Milan, Italy, showed a significant association between urinary catheter use and the incidence of MDROS with a P-value of 0.006. In addition, Nicolo et al. also studied other risk factors associated with ESBL + bacteria (P=0.008), one of which was the use of invasive devices that remain in the patient's body, such as urinary catheters, nasogastric tubes, and gastrotomy tubes **(11)**. A study at Soetomo Surabaya General Hospital 2008 showed that patients with catheters were at risk of ESBL-producing *E. coli* and *K. pneumoniae* bacteria. This is because urinary catheters can cause germs to form ESBLs that are resistant to antibiotics **(22)**. Urinary catheter use can cause bacterial colonization and produce biofilms that are persistent, recurrent, resistant to antibiotics, and can increase mortality. Moreover, inserting urinary catheters can cause urethral injury, which will be the site for bacterial adhesion, leading to the incidence of MDROs due to antibiotic resistance **(23)**.

The fact that there was no statistically significant correlation between other variables and the incidence of MDROs in this study was caused by the different sensitivity patterns of the causative bacteria compared to other studies. In this study, the most common bacteria found in all specimens were *K. pneumoniae, E. coli*, and *Staphylococcus aureus*. In contrast, the specimens in this study were predominantly from sputum, blood, and urine.

Table 5. Logistic regression analysis (OR) of sepsis patients due to MDROs

Characteristics	MDROs criteria		Unadjusted OR			Adjusted OR		
	MDROs n=83 (%)	Non MDROs n=41 (%)	OR	95% CI	p	OR	95% CI	p
Age			1.033	0.476-2.244	1.000	1.233	0.423-3.592	0.702
18 – 65 years	52 (62.7)	26 (63.4)						
> 65 years	31 (37.3)	15 (36.6)						
Gender			1.306	0.616-2.769	0.614	1.300	0.455-3.741	0.624
Male	48 (57.8)	21 (51.2)						
Female	35 (42.2)	20 (48.8)						
Severity Of Illness (SOFA Score)								
1 - 6	35 (42.2)	18 (43.9)			0.932			0.937
7 – 12	38 (45.8)	17 (41.5)	1.150	0.513-2.575		0.705	0.217-2.289	0.561
13 – 18	9 (10.8)	5 (12.2)	0.926	0.270-3.174		0.973	0.159-5.959	0.976
19 – 24	1 (1.2)	1 (2.4)	0.514	0.030-8.710		0.570	0.016-20.402	0.758
Body mass index								
Normal	44 (53.0)	18 (43.9)			0.633			0.470
Underweight	24 (28.9)	14 (34.1)	0.701	0.298-1.653		0.651	0.221-1.919	0.437
Overweight-Obese	15 (18.1)	9 (22.0)	0.682	0.253-1.838		0.459	0.126-1.675	0.239
History of antibiotic use			2.641	1.207-5.776	0.024	3.016	1.038-8.759	0.042*
Yes	61 (73.5)	21 (51.2)						
No	22 (26.5)	20 (48.8)						
Medical Devices								
Urine catheter	76 (91.6)	31 (75.6)	3.502	1.233-10.032	0.031	74.762	2.086-2680.05	0.018*
Nasogastric tube	70 (84.3)	30 (73.2)	1.974	0.795-4.904	0.215	0.097	0.002-1.682	0.097
Endotracheal tube	4 (4.8)	0 (0.0)	N/A	N/A	0.374	N/A	N/A	
Thorax tube	0 (0.0)	1 (2.4)	N/A	N/A	0.718	N/A	N/A	
Comorbidity	**(n=89)**							
Chronic kidney disease	25	13	0.928	0.414-2.082	1.000	N/A	N/A	
Type 2 Diabetes mellitus	17	10	0.798	0.328-1.945	0.791	0.302	0.030-3.015	0.308
Malignancy	11	10	0.474	0.182-1.230	0.193	0.419	0.114-1.539	0.190
Stroke	9	3	1.541	0.394-6.026	0.763	0.561	0.092-3.404	0.530
Hypertension	8	2	2.080	0.421-10.272	0.572	0.280	0.075-1.047	0.058
Heart failure	8	8	0.440	0.152-1.273	0.203	0.677	0.089-5.121	0.705
Chronic liver disease	5	4	0.593	0.150-2.338	0.700	0.573	0.102-3.231	0.528
Chronic lung disease	4	1	2.025	0.219-18.724	0.882	0.161	0.003-7.467	0.351
Autoimmune disease	1	0	N/A	N/A	1.000	N/A	N/A	
HIV	1	0	N/A	N/A	1.000	N/A	N/A	

Abbreviation: MDROs = multidrug-resistant organisms, OR = odd ratio, HIV = human immunodeficiency virus, N/A = not available. *Significant risk factor at *P*<0.05

None of the comorbid diseases were significantly correlated with the incidence of infection due to MDROs in sepsis patients (Table 5). A study at Dr. Moewardi Surakarta Hospital showed similar results: no statistically significant relationship was found between gender, age, and comorbid diseases, including CHF, COPD, Diabetes Mellitus, and AIDS **(14)**.

Among the risk factors for MDROs in sepsis patients at Dr. M. Djamil General Hospital, using urinary catheters with OR = 74.76 (2.086-2680.05) was the strongest risk factor associated with infection due to MDROs in sepsis patients. Another strong risk factor for MDROs was the history of antibiotic use with an OR=3.016 (1.038-8.759), as shown in Table 5.

Urinary catheter use was the strongest risk factor associated with infection due to MDROs in sepsis patients with OR=74.76 (2.086-2680.05). In line with the study by Nicolo et al. in 2014 in Milan, urinary catheters are a risk factor that has a strong impact on the occurrence of infections due to MDROs with an OR = 1.9 (0.9-3.9) **(24)**. Another study at the Royal London Hospital, UK, in 2017 showed that using urinary catheters increased the risk of severe sepsis with an OR of 3.94 (1.70-9.11) **(25)**.

Another strong risk factor for MDROs is a history of antibiotic use with an OR of 3.016 (1.038-8.759). In 2016, a study conducted at Aichi Medical University Hospital, Japan discussing the prevalence and risk factors for ESBL infection which showed the results of a history of antibiotic use with aminoglycosides with an OR of 5.17 (0.14-1.43), oxazolidinone OR = 25, 5 (0.23-3.39), tetracycline OR=26.80 (1.27-2.03),

fluoroquinolone OR=5.59 (0.33-1.40), second-generation cephalosporin OR=2.98 (0.18-0.89) and fourth generation OR54.73 (1.70-2.32) are strong risk factors for colonization and infection with ESBL-producing Enterobacteriaceae **(26)**. In 2021, a study by Tianjin Medical University, China, which discussed the risk factors for MDROs in patients with diabetic foot ulcer infection, showed that the history of antibiotic use had a strong effect on infection due to MDROs with an OR value of 1.17 (0.63-2.20) **(27)**.

4. Conclusion

It was concluded that the history of antibiotic use and the use of urinary catheters were the strongest factors affecting infection due to MDROs. The suggestion in this study is that antibiotics should be used wisely and rationally in the management of infectious patients. The use of urinary catheters should be done more selectively for inpatients to prevent the development of MDROs as a cause of infection, and further studies should be continued with a wider population of infectious patients, to analyze the factors that influence infection in various types of MDROs (ESBL, CRO, MRSA, VRE).

Acknowledgment

Thank you to the Education and Research Department of Dr. M. Djamil Padang General Hospital for supporting this research by providing input and consultation throughout the study. We also thank the laboratory of Dr. M. Djamil Padang General Hospital for supporting and assisting in providing data and information for the study.

Conflict of Interest

The authors declared no conflict of interest.

Authors' Contribution

Study concept and design: Fadrian; Supervision of the study: Fadrian, Linosefa; Materials: Fadrian, Linosefa, Muhammad Ridhwan F, Hidayatul Hasnah; Data collection and/or processing: Fadrian, Linosefa, Hidayatul Hasnah; Analysis and interpretation: Fadrian, Linosefa, Muhammad Ridhwan F; Literatur review: Fadrian, Linosefa; Writing: Fadrian, Linosefa, Muhammad Ridhwan F, Alya Syafa Ayuni; Critical review: Fadrian, Linosefa.

Funding

The Education and Research Department of Dr. M. Djamil Padang General Hospital funds this study.

Reference

1. Frieden T. Antibiotic Resistance Threats in the United States, 2013. United States. Centers for Disease Control and Prevention. 2013. p. 1-114.
2. Estiningsih D, Puspitasari I, Nuryastuti T. Identifikasi infeksi multidrug-resistant organisms (MDRO) pada pasien yang dirawat di bangsal neonatal intensive care unit (NICU) rumah sakit. J Manage Pharm Pract. 2016;6(3):243-8.
3. Fadrian F, Chen K, Kumalawati J, Rumende CM, Shatri H, Nelwan EJ. The Validation of Drug Resistance in Pneumonia (DRIP) Score in Predicting Infections due to Drug-Resistant Pathogens in Community-acquired Pneumonia at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Acta Med Indones. 2021;53(4):416-22.
4. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81. [DOI:10.1111/j.1469-0691.2011.03570.x] [PMID]
5. Chitnis AS, Caruthers PS, Rao AK, Lamb J, Lurvey R, De Rochars VB, et al. Outbreak of Carbapenem-Resistant Enterobacteriaceae at a Long-Term Acute Care Hospital: Sustained Reductions in Transmission through Active Surveillance and Targeted Interventions. Infect Control Hosp Epidemiol. 2012;33(10):984-92. [DOI:10.1086/667738] [PMID]
6. Center for Disease Dynamics E& P. State of the World's Antibiotics. Washington D. C.: CDDEP; 2015. 1–84.
7. Dwiprahasto I. Kebijakan untuk Meminimalkan Risiko Terjadinya Resistensi Bakteri di Unit Perawatan Intensif Rumah Sakit. J Manajemen Pelay Kesehatan. 2005;8(04):177-81.
8. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. Ann Intensive Care. 2011;1(1): 47. [DOI:10.1186/2110-5820-1-47] [PMID] [PMCID]

9. Basak S, Singh P, Rajurkar M. Multidrug Resistant and Extensively Drug Resistant Bacteria: A Study. J Pathol. 2016;2016:4065603. [DOI:10.1155/2016/4065603] [PMID] [PMCID]
10. Ajeng FSK, Prijono S, Novita A. Risk Difference of Multidrug Resistance Organisms (MDROs) According to Risk Factor and Hand Hygiene Compliance. J Berkala Epidemiol. 2015;3(3):277-89. [DOI:10.20473/jbe.V3I32015.277-289]
11. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;7: 2050312119835043. [PMID] [PMCID] [DOI:10.1177/2050312119835043]
12. Capsoni N, Bellone P, Aliberti S, Sotgiu G, Pavanello D, Visintin B, et al. Prevalence, risk factors and outcomes of patients coming from the community with sepsis due to multidrug resistant bacteria. Multidiscip Respir Med. 2019;14(23). [DOI:10.4081/mrm.2019.23] [PMID] [PMCID]
13. Wijaksana DS, Anggraeni N, Endriani R. Pola Bakteri dan Resistensi Antibiotik pada Pasien Sepsis di Intensive Care Unit (ICU) RSUD Arifin Achmad Provinsi Riau Periode 1 Januari-31 Desember 2017. J Ilmu Kedokt. 2019;13(2):46-54. [DOI:10.26891/JIK.v13i2.2019.46-54]
14. Raniputri KA, Harsini H, Reviono R, Saptawati L. Correlation of Antibiotic Resistance with Sepsis Incidence, Hospital Mortality, and Time of Sepsis Onset in Community Acquired Bacterial Pneumonia. J Respirol Indones. 2022;42(3):184-90. [DOI:10.36497/jri.v40i3.359]
15. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18(6):596. [PMID] [PMCID] [DOI:10.1186/s13054-014-0596-8]
16. Fuchs A, Tufa TB, Hörner J, Hurissa Z, Nordmann T, Bosselmann M, et al. Clinical and microbiological characterization of sepsis and evaluation of sepsis scores. Plos One. 2021;16(3):e0247646. [PMCID] [DOI:10.1371/journal.pone.0247646] [PMID]
17. Strich JR, Heil EL, Masur H. Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. J Infect Dis. 2020;222(Supplement_2):S119-S31. [DOI:10.1093/infdis/jiaa221] [PMID] [PMCID]
18. Agatha C, Liana P, Susilawati S. Perbedaan Angka Kejadian Multidrug Resistant Organisms Tahun 2015 Dan 2016 Pada Pasien Gicu Rsup Dr. Mohammad Hoesin Palembang. Majalah Kedokteran Sriwijaya. 2018;50(3):105-14.
19. Li Z, Zhang Y, Zhang W, Zhang Y, Zhou S, Chen W, et al. Study on the Detection and Infection Distribution of Multidrug-Resistant Organisms in Different Specimens. Infect Drug Resis. 2022;15: 5945-52. [DOI:10.2147/IDR.S375682] [PMID] [PMCID]
20. Kim B, Kim Y, Hwang H, Kim J, Kim SW, Bae IG, et al. Trends and correlation between antibiotic usage and resistance pattern among hospitalized patients at university hospitals in Korea, 2004 to 2012: A nationwide multicenter study. Medicine. 2018;97(51):e13719. [PMID] [PMCID] [DOI:10.1097/MD.0000000000013719]
21. Kolár M, Urbánek K, Látal T. Antibiotic selective pressure and development of bacterial resistance. Int J Antimicrob Agents. 2001;17(5):357-63. [DOI:10.1016/S0924-8579(01)00317-X] [PMID]
22. Husada S, Hardjowijoto S, Gardjito W. Perbandingan Dan Penyebaran Escherichia coli Dan Klebsiella Pneumoniae Penghasil Extended Spectrum Beta-Laktamase Pada Isolat Urine Pasien Pria Dengan Kateter Dan Tanpa Kateter. Int J Urol. 2014;15(1):15-20. [DOI:10.32421/juri.v15i1.364]
23. Kırmusaoğlu S, Yurdugül S, Metin A, Vehid S. The effect of urinary catheters on microbial biofilms and catheter associated urinary tract infections. Urol J. 2017;14(2):3028-34.
24. El mekes A, Zahlane K, Ait said L, Tadlaoui Ouafi A, Barakate M. The clinical and epidemiological risk factors of infections due to multi-drug resistant bacteria in an adult intensive care unit of University Hospital Center in Marrakesh-Morocco. J Infect Public Health. 2020;13(4):637-43. [DOI:10.1016/j.jiph.2019.08.012] [PMID]
25. Melzer M, Welch C. Does the presence of a urinary catheter predict severe sepsis in a bacteraemic cohort? J Hosp Infect. 2017;95(4):376-82. [DOI:10.1016/j.jhin.2017.01.003] [PMID]
26. Nakai H, Hagihara M, Kato H, Hirai J, Nishiyama N, Koizumi Y, et al. Prevalence and risk factors of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. J Infect Chemother. 2016;22(5):319-26. [DOI:10.1016/j.jiac.2016.02.004] [PMID]
27. Liu X, Ren Q, Zhai Y, Kong Y, Chen D, Chang B. Risk Factors for Multidrug-Resistant Organisms Infection in Diabetic Foot Ulcer. Infect Drug Resist. 2022;15:1627-35. [DOI:10.2147/IDR.S359157] [PMID] [PMCID]