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ASSOCIATION BETWEEN MULTIDRUG-RESISTANT ORGANISMS (MDROS) AND MORTALITY IN SEPSIS PATIENT AT RSUP DR. M. DJAMIL PADANG

Alya Syafa Ayuni [1], Fadrian Fadrian [2*], Erlina Rustam [3], Linosefa [4], Rahmatini [3], Arina Widya Murni [2]

[1.] Medical Education Study Program, Faculty of Medicine Andalas University, Padang, Indonesia

[2.] Departement of Internal Medicine, Faculty of Medicine Andalas University, Padang, Indonesia

[3.] Departement of Pharmacology, Faculty of Medicine Andalas University, Padang, Indonesia

[4.] Departement of Microbiology, Faculty of Medicine Andalas University, Padang, Indonesia

[*]e-mail: fadrian@med.unand.ac.id

ABSTRACT

Multidrug-resistant organisms (MDROs) is a condition where bacteria are resistant to at least 1 type of antibiotic from ≥3 classes of antibiotics. Bacteria are one of the causes of infection. If the treatment of infection is not optimal, it can cause patients to experience a more severe condition, that is sepsis. Sepsis is the leading cause of death from infection. This study aimed to determine the association between Multidrug-Resistant Organisms (MDROs) and mortality in sepsis patients.This study is an analytical study with a cross-sectional design using secondary data sourced from medical record data of hospitalized sepsis patients in the internal medicine section of RSUP Dr. M. Djamil Padang in 2022. The sampling technique was total sampling. The number of samples that met the criteria was 99 samples. Data analysis used a chi-square test. The results of this study showed that sepsis patients were dominated by female (55.6%), aged ≥60 years (55.6%), with the most common source of infection being the respiratory system (83.8%), and the use of the most used medical device was NGT (90.9%), the outcome of death in sepsis patients was 53 patients (53.5%). Multidrug-resistant organisms (MDROs) bacteria that cause the most sepsis patients are ESBL-producing Klebsiella pneumoniae as many as 29 isolates (39.2%) with the most specimen collection is sputum, which is 40 specimens (54.1%). Multidrug-resistant organisms (MDROs) bacteria in sepsis patients with the highest death outcome were ESBL-producing Escherichia coli with 16 isolates (21.6%). The results of the Chi-square test of multidrug-resistant organisms (MDROs) bacteria with sepsis patient mortality in this study obtained a value of p=0.743. This study concludes that there is no significant association between multidrug-resistant organisms (MDROs) and mortality in sepsis patient

Keywords : Sepsis, Multidrug-resistant organisms (MDROs), mortality

INTRODUCTION

Infection is a condition where the entry of pathogenic microorganisms, such as viruses, bacteria, fungi, and parasites, into the body can cause illness. One of the treatments for someone with an infection is the administration of antimicrobial agents, such as antibiotics. Antibiotics are treatments used for infections caused by bacteria. Giving antibiotics that are not by the dose and duration of administration can cause antibiotics to be inadequate to overcome pathogenic bacteria. This can occur because bacteria begin to be resistant to antibiotics.[1]

Multidrug-resistant organisms (MDROs) is a condition where microorganisms, generally bacteria, are resistant to at least one type of antibiotic from three or more classes of antibiotics.[2] Based on data from the World Health Organization (WHO) in the Antimicrobial Resistance: Global Report on Surveillance, Southeast Asia has the highest number of antibiotic resistance cases in the world, especially infections caused by methicillin-resistant Staphylococcus aureus.[3] Based on data from a national survey of antimicrobial resistance conducted by the Ministry of Health in 2016, the prevalence of multidrug-resistant organisms (MDROs) of ESBL-producing Escherichia coli and Klebsiella pneumoniae bacteria was 50-82%.[1] Based on the data obtained in the Antibiogram of Dr. M. Djamil Padang Hospital in 2022, it was found that the most MDROs in hospitalized patients were ESBL-producing Klebsiella pneumoniae by 10.8% and ESBL-producing E.coli by 10.3%.[4] Infections caused by antibiotic-resistant bacteria can cause treatment to be not optimal and can lead to sepsis.[5]

Sepsis is the leading cause of death from infection if not immediately recognized and treated.[6] In 2017, sepsis cases reached 48.9 million cases with a total mortality of 11 million worldwide.[7] Research conducted at Dr. M. Djamil Padang Hospital in 2020-2021 found that the mortality rate of sepsis patients was 26.2%.[8] Sepsis is one of the important health problems to be considered because of

the relatively high mortality rate in the world. Based on this description, researchers are interested in finding out whether there is a relationship between multidrug-resistant organisms (MDROs) and mortality in sepsis patients. This study aims to determine the relationship between multidrug-resistant organisms (MDROs) and mortality in sepsis patients.

RESEARCH METHODS

This study is an analytic study using a cross-sectional study design. This research was conducted at the Medical Record Installation of Dr. M. Djamil Padang Hospital in January 2024. The population in this study were all adults patients diagnosed with sepsis who were treated in the Internal Medicine of Dr. M. Djamil Padang. The sample of this study used medical record data of adult patients diagnosed with sepsis who were treated in the Internal Medicine section of Dr. M. Djamil Padang Hospital in the period August 2022-December 2022. The sampling technique used total sampling, which is a sampling technique as a whole from a population that meets the inclusion criteria of the study. The inclusion criteria of this study were all patients admitted to the Internal Medicine section of Dr. M. Djamil Padang Hospital with a diagnosis of sepsis in the period August 2022-December 2022, patients aged ≥ 18 years, patients who had data on bacterial culture results, and patients who had antibiotic sensitivity test data. Exclusion criteria in this study were incomplete data in accordance with the research variables and patients who refused to do bacterial culture. In this study, 99 patients with 112 isolates who met the inclusion criteria were obtained. All samples were included as a source of research data.

The data that has been collected will be processed and analyzed using Microsoft Excel and SPSS using the Chi-square test. This research has passed the ethical review with letter number DP.04.03/D.XVI.XI/621/2023.

RESULTS

The number of samples that met the inclusion criteria was 99 patients with 112 isolates because some patients had more than 1 type of bacteria.

Table 1. Characteristics of Sepsis Patiens

Characteristics	Frequency (n=99)	Percentage %
Gender		
Male	44	44.4
Female	55	55.6
Age Group		
18-40 years	10	10.1
>40- 60 years	34	34.3
>60 years	55	55.6
Focus of infection		
Respiratory System	83	83.8
Skin and Soft Tissue	7	7.1
Digestive System	2	2.0
Urinary System	7	7.1
Use of Medical Device		
NGT	90	90.9
Urine Catheter	88	88.9
Mechanical Ventilator	21	21.2

Table 1 shows that sepsis patients are dominated by female (55.6%), elderly patients (>60 years) (55.6%), the most common source of infection in the respiratory system (83.8%) and the most use of medical devices is NGT (90.9%).

Table 2. Frequency Distribution of Sepsis Patient Mortality

Mortality of Sepsis Patients	Frequency (n=99)	Percentage %
Passed-away	53	53.5
Survived	46	46.5
Total	**99**	**100**

Table 2 shows that there were 53 cases (53.5%) of passed-away sepsis patients within 14 days of treatment in the internal medicine department of Dr. M. Djamil Padang Hospital in 2022.

Table 3. Frequency Distribution of Bacterial Isolates of Multidrug-Resistant Organisms (MDROs) in Sepsis Patients

Causative Microorganisms	Specimen (n=74)					Total (%)
	Blood (%)	Sputum (%)	Pus (%)	Urin (%)	Feces (%)	
ESBL-Producing *Escherichia coli*	0 (0.0)	11(14.9)	2 (2.7)	9(12.2)	2(2.7)	24(32.4)
ESBL-Producing *Klebsiella pneumoniae*	1 (1.4)	20(27.0)	3 (4.1)	5 (6.8)	0 (0.0)	29(39.2)
Carbapenemase-Producing *Escherichia coli*	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.4)
Carbapenemase-Producing *Klebsiella pneumoniae*	0 (0.0)	3 (4.1)	1 (1.4)	0 (0.0)	1 (1.4)	5 (6.8)
MRSA	8 (10.8)	6 (8.1)	1 (1.4)	0 (0.0)	0 (0.0)	15(20.3)
Total	**9 (12.2)**	**40(54.1)**	**7 (9.5)**	**15(20.3)**	**3 (4.1)**	**74 (100)**

Table 3 shows that the most causative MDROs bacteria in sepsis patients were ESBL-producing Klebsiella pneumoniae (39.2%) and the specimen with the most MDROs bacterial isolates was sputum (54.1%).

Table 4. Frequency Distribution of Bacterial Multidrug-Resistant Organisms (MDROs) Causes with Mortality in Sepsis Patients

Causative Microorganisms	Outcome (n=74)		Total (%)
	Passed-Away (%)	Survived (%)	
ESBL-Producing *Escherichia coli*	16 (21.6)	8 (10.8)	24 (32.4)
ESBL-Producing *Klebsiella pneumoniae*	14 (18.9)	15 (20.3)	29 (39.2)
Carbapenemase-Producing *Escherichia coli*	0 (0.0)	1 (1.4)	1 (1.4)
Carbapenemase-Producing *Klebsiella pneumoniae*	0 (0.0)	5 (6.8)	5 (6.8)
MRSA	7 (9.5)	8 (10.8)	15 (20.3)
Total	**37 (50.0)**	**37 (50.0)**	**74 (100)**

Table 4 shows that the MDROs bacteria that caused the most mortality in sepsis patients were ESBL-producing Escherichia coli (21.6%).

Table 5. Association Between Multidrug-Resistant Organisms (MDROs) and Mortality in Sepsis Patients

***Multidrug-Resistant Organisms* (MDROs)**	Outcome (n=112)		Total (%)	*p-value*
	Passed-Away (%)	Survived (%)		
MDROs	37 (33.0)	37 (33.0)	74 (66.1)	0.743
Non-MDROs	21 (18.8)	17 (15.2)	38 (33.9)	
Total	**58 (51.8)**	**54 (48.2)**	**112 (100)**	

Table 5 shows that there is no significant association between multidrug-resistant organisms (MDROs) and mortality in sepsis patients (p>0.05).

DISCUSSION

Characteristics of Sepsis Patiens

The results showed that based on gender, sepsis patients were mostly dominated by female as many as 55 patients (55.6%). This is in line with research conducted by Suwondo in the ICU of Dr. Kariadi Hospital Semarang, which showed that the majority of sepsis patients were female as many as 41 patients (53.2%).[9] There are differences in the immune system in male and female. This is because the hormone estrogen in female stimulates immune activity, while the hormone testosterone in male suppresses the immune system.[10] However, estrogen levels may decrease with age. Estrogen levels in female are lower after menopause. In elderly female, a decrease in estrogen can lead to a decrease in the immune system, which can be seen as an increase in inflammation in female with advanced age. Therefore, elderly female are more susceptible to infections.[11]

Inpatient sepsis patients were dominated by elderly patients, aged >60 years as many as 55 patients (55.6%). The oldest patient's age was 91 years and the youngest patient's age was 20 years. This is in line with research conducted by Wicaksono in a type B private hospital in

South Tangerang showing that the majority of patients were ≥ 60 years old (60%).[12] As we age, there will be a decline in the immune system. The decline in the immune system due to age is also known as immunosenescence. There will be changes in the immune system such as a decrease and dysregulation of the immune system. Immunosenescence affects the innate immune system, which consists of monocytes, natural killer (NK) cells and dendritic cells, as well as the adaptive immune system, which consists of B lymphocytes and T lymphocytes. This results in the elderly being more at risk of infection.[13,14]

The results showed that the source of infection most experienced by patients was dominated by the respiratory system as many as 83 patients (83.8%). This is in line with research conducted by Fataya conducted at Dr. M. Djamil Padang Hospital in 2020-2021, it was found that the most sources of infection came from the lungs as many as 116 patients (80%).[8] The respiratory system is the most common source of infection. The respiratory system is the entry point for the external environment into the body. Several factors influence the occurrence of pulmonary infections, such as age, lung anatomical abnormalities, decreased and less effective mucociliary clearance, and decreased immune system.[15–17] In the elderly there can be a decrease in mucociliary clearance, this is due to the slowing of the frequency of ciliary movements. Therefore, the elderly are susceptible to pulmonary infection.[17]

The results showed that the most common use of medical devices in sepsis patients was the use of NGT as many as 90 people (90.2%). This is different from research conducted by Suwondo (2015) at Dr. Kariadi Semarang General Hospital. The results of this study found that the highest use of medical devices in sepsis patients was the use of mechanical ventilators, namely 74 people (67.9%). The study conducted by Suwondo was conducted on 77 people and there was no data on the use of medical devices in the form of NGT in the study.[9] NGT (naso gastric tube) is a special tube inserted through the nose that is used to introduce food, fluids in dysphagia patients. However, NGT may increase patient morbidity and mortality.[18] The use of NGT is one of the factors for nosocomial respiratory infections. NGT can increase oropharyngeal colonization, reflux, and bacterial migration. NGT is one of the causes of aspiration pneumonia. The occurrence of respiratory system infections in patients using NGT may occur due to vomiting and aspiration of gastric contents. The use of NGT may increase the incidence of respiratory system infections.[19,20]

Sepsis Patients Mortality

The results of this study showed that the frequency distribution of mortality of inpatient sepsis patients in the internal medicine department of Dr. M. Djamil Padang Hospital from August 2022 to December 2022 was 53 patients (53.5%). In this study, of the 53 patients who died of sepsis, 30 patients were aged> 60 years and were dominated by women as many as 33 patients. This is in line with research conducted by Manapa in several hospitals in Indonesia from 2003 to 2019, obtained from 1178 patients, 617 patients died (52.4%).[21] In 2017, there were an estimated 11 million total deaths caused by sepsis worldwide, representing 19.7% of all deaths worldwide. A total of 5.89 million deaths from sepsis were due to infectious infections.[7] Various factors cause mortality in sepsis patients, one of which is age. In the elderly, the body will experience a decrease in the immune system, so the elderly are more susceptible to infection.[13,14,22] Another factor that affects sepsis mortality is gender. Female have the hormone estrogen, which stimulates immune system activity. As female age, the estrogen hormone will decrease, resulting in a decrease in the immune system in female. This can cause elderly female to be more susceptible to infection. [10,11,23]

Multidrug-resistant organisms (MDROs) Bacterial Isolates Causing Sepsis Patients

Based on the results of the study, the dominant multidrug-resistant organisms (MDROs) bacteria that cause sepsis are ESBL-producing *Klebsiella pneumoniae* as many as 29 isolates (39.2%), followed by ESBL-producing *Escherichia coli* as many as 24 isolates (32.4%), and MRSA as many as 15 isolates (20.3%). This study is in line with the data obtained from the antibiogram of Dr. M. Djamil Padang Hospital in 2022. In the antibiogram data, it was found that the most MDROs in hospitalized patients were ESBL-producing *Klebsiella pneumoniae* at 10.8%.[4] As many as 60-70% of sepsis cases are caused by gram-negative bacteria. The outer membrane of gram-negative bacteria consists of lipopolysaccharide (LPS). LPS stimulates the release of proinflammatory mediators that can lead to systemic and tissue inflammation.[24] *Enterobacteriaceae* are a common cause of community-onset infections as well as nosocomial infections and these bacteria are generally susceptible to antibiotic resistance.[25] *Escherichia coli* and *Klebsiella pneumoniae* are the bacteria from the *Enterobacteriaceae* family that cause the most infections and the bacteria that cause the most antibiotic resistance, that are beta lactamase (ESBL) enzyme producers.[26,27]

The most specimens taken were sputum as many as 40 specimens (54.1%), followed by urine as many as 15 specimens (20.3%), blood as many as 9 specimens (12.2%), pus as many as 7 specimens (9.5%), and feces as many as 3 specimens (4.1%). This is in line with research conducted by Wijaksana at Arifin Achmad Riau Hospital, where culture specimens with the most bacterial growth were sputum as many as 25 specimens (67.57%).[28] Sputum is the most commonly collected specimen compared to other specimens. This indicates that many bacteria are found in the airway. The high collection of sputum specimens in the internal medicine ward can occur due to the use of medical devices such as NGT and mechanical ventilator which are risk factors for airway infections.[29–31]

Multidrug-resistant organisms (MDROs) Bacteria with Sepsis Patient Mortality

Based on the data obtained from 74 culture examinations performed, the most multidrug-resistant organisms (MDROs) bacteria that caused the patient to die

were ESBL-producing *Escherichia coli* as many as 16 isolates (21.6%), followed by ESBL-producing *Klebsiella pneumoniae* as many as 14 isolates (18.9%), and MRSA as many as 7 isolates (9.5%). This study is in line with research conducted by Sakellariou (2016) in a tertiary hospital in Berlin, Germany. In the study, it was stated that the most common cause of multidrug-resistant organisms (MDROs) in sepsis patients was ESBL-producing *Escherichia coli* as many as 45 (55.6%) and also the cause of most mortality, as many as 38 (70.4%).[32] Gram-negative bacteria are a public health problem due to their high resistance to antibiotics.[33] The outer membrane of gram-negative bacteria is the cause of resistance. Any changes to the outer membrane of gram-negative bacteria, such as changing hydrophobic properties or mutations in porins can make the bacteria resistant. Gram-positive bacteria do not have an outer membrane like gram-negative bacteria, which is what makes gram-negative bacteria more resistant to antibiotics.[34] Various factors can lead to higher mortality caused by gram-negative bacteria, such as patient and disease factors, especially in patients with older age, nosocomial infections experienced by patients, and the severity of the disease suffered by patients.[35]

Association Between Multidrug-resistant organisms (MDROs) and Mortality in Sepsis Patients

The results of this study found that there was no significant relationship between multidrug-resistant organisms (MDROs) and mortality. This can be seen from the p value> 0.05 (p=0.743). This is in line with research conducted by Al-Sunaidar (2022) conducted in Malaysian tertiary hospitals in 2022. The study found that there was no significant relationship between multidrug-resistant organisms (MDROs) and mortality in sepsis patients (p=0.354).[36] The absence of a significant relationship between multidrug-resistant organisms (MDROs) and mortality in sepsis patients suggests that other factors influence mortality in sepsis patients. Research conducted by Velez stated that the source of infection is one of the risk factors for mortality in sepsis patients. In this study, it was found that infections in the bloodstream and infections in the skin / tissue were risk factors for mortality in sepsis. Organ dysfunction and also the severity of a person assessed using the SOFA score are also risk factors for mortality in sepsis patients. In addition, successful antibiotic therapy and antibiotic de-escalation are other risk factors for mortality in sepsis patients.[37] Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021, provides recommendations for immediate administration of broad-spectrum antibiotic therapy in the first 1 hour for sepsis patients. Giving broad-spectrum antibiotic therapy in the first 1 hour is one of the most effective interventions to reduce mortality in sepsis patients.[38] Other risk factors are low platelet count, elevated CRP, elevated serum lactate, elevated d-dimer, elevated creatinine, prothrombin time (PT), and decreased albumin. Patient comorbidities such as renal, hepatic, metastasized malignant tumors, and congestive heart failure are also risk factors that increase mortality in sepsis patients.[39–41]

CONCLUSION

Based on the research that has been done, it can be concluded that most sepsis patients are female, aged >60 years, with the respiratory system as the most common source of infection, and the most used medical device is NGT. More than half of the hospitalized sepsis patients died. The most common multidrug-resistant organisms (MDROs) causing bacteria were ESBL-producing Klebsiella pneumoniae with the largest number of specimens being sputum. ESBL-producing Escherichia coli was the most common multidrug-resistant organisms (MDROs) causing mortality in sepsis patients. There was no significant relationship between multidrug-resistant organisms (MDROs) and mortality in sepsis patients.

REFERENCES

1. Menteri Kesehatan Republik Indonesia. Peraturan Menteri Kesehatan Republik Indonesia nomor 28 tahun 2021 tentang pedoman penggunaan antibiotik. Jakarta: Menkes RI;2021.
2. Estiningsih D, Puspitasari I, Nuryastuti T. Identifikasi infeksi multidrug-resistant organisms (MDROs) pada pasien yang dirawat di bangsal neonatal intensive care unit (NICU) RSUP DR. Soeradji Tirtonegoro Klaten. JMPF. 2016;6(3):243–8.
3. Morrison L, Zembower TR. Antimicrobial resistance. Gastrointest Endosc Clin N Am. 2020;30(4):619–35.
4. Laboratorium Mikrobiologi Klinik. Antibiogram RSUP Dr. M. Djamil Padang tahun 2022. Padang: RSUP Dr. M. Djamil;2022.
5. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):4–11.
6. Singer M, Deutschman CS, Seymour C, Shankar Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–10.
7. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet. 2020;395(10219):200–11.
8. Fataya E, Fadrian, Mustafa Noer, Dwitya Elvira, Yuliarni Syafrita, Netti Suharti. Characteristics of adult sepsis patients admitted to Department of Internal Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia. Biosci Med J Biomed Transl Res. 2023;7(3):3191–8.
9. Suwondo VN, Dwi Jatmiko H, Hendrianingtyas M. Karakteristik dasar pasien sepsis yang meninggal ICU RSUP Dr. Kariadi Semarang periode 1 Januari-31 Desember 2014. MMM. 2015;4(4):1586–96.
10. Wilson C. Are there sex differences in the immune system? New Sci. 2023;
11. Harding AT, Heaton NS. The impact of estrogens

and their receptors on immunity and inflammation during infection. Cancers (Basel). 2022;14(4):1–16.
12. Wicaksono A, Adisasmita A, Harijanto E. Frekuensi dan mortalitas pasien sepsis dan syok sepsis di ICU rumah sakit swasta tipe B di Tangerang Selatan. J Epidemiol Kesehat Indones. 2022;6(1):13–20.
13. Fuentes E, Fuentes M, Alarcón M, Palomo I. Immune system dysfunction in the elderly. An Acad Bras Cienc. 2017;89(1):285–99.
14. Siregar FM. Immunosenescence : penuaan pada sel makrofag. JIK. 2019;13(1):14.
15. Kradin RL, Mark EJ. Pathology of pulmonary infection. In: Diagnostic Pathology of Infectious Disease. 2018. p. 143–206.
16. Ann E. McCullough M, Kevin O. Leslie M. Lung infections. In: Practical Pulmonary Pathology. 2017. p. 147–70.
17. Hasan H, Arusita M R. Perubahan fungsi paru pada usia tua. J Respirasi. 2017;3(2):52–7.
18. Hsu CY, Lai JN, Kung WM, Hung CH, Yip HT, Chang YC, et al. Nationwide prevalence and outcomes of long-term nasogastric tube placement in adults. Nutrients. 2022;14(9).
19. Van Schayck CP, Mommers M, Dompeling ED. Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patiens. Eur Respir J. 2006;27(2):435–6.
20. Meriyanti, Rohana N, Windyastuti. Penggunaan nasogatric tube berhubungan dengan terjadinya pneumonia. J Ners Widya Husada. 2020;4(1):1–8.
21. Manapa AM. Karakteristik penderita sepsis yang dirawat di beberapa rumah sakit di Indonesia periode tahun 2003 sampai dengan tahun 2019. Universitas Bosowa; 2020.
22. Sanjaya BD, Djuang MH, Muniro FD, Chiuman L. Sepsis risk factors in elderly patients at Royal Prima Medan general hospital. Jambura J Heal Sci Res. 2022;4(3):596–603.
23. Chen C, Wu X, Zhang W, Pu Y, Xu X, Sun Y, et al. Predictive value of risk factors for prognosis of patients with sepsis in intensive care unit. Med (United States). 2023;102(23):E33881.
24. Menteri Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan Republik Indonesia nomor HK.01.07/MENKES/342/2017 tentang pedoman nasional pelayanan kedokteran tata laksana sepsis. Jakarta: Menkes RI;2017.
25. Van Duin D, Paterson DL. Multidrug-Resistant Bacteria in the Community: Trends and Lessons Learned. Infect Dis Clin North Am. 2016;30(2):377–90.
26. CDC. Public health strategies to prevent the spread of novel and targeted multidrug- resistant organisms (MDROs). 2023;
27. Kang CI, Song JH. Antimicrobial resistance in Asia: Current epidemiology and clinical implications. Infect Chemother. 2013;45(1):22–31.
28. 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.
29. Agatha C, Liana P, Susilawati. Perbedaan angka kejadian multidrug resistant organisms tahun 2015 dan 2016 pada pasien GICU RSUP Dr. Mohammad Hoesin Palembang. Maj Kedokt Sriwij. 2018;3(Juli):105–14.
30. Lestari PI, Ika S, Huda R. The sensitivity pattern of bacteria against antibiotics at the intensive care unit of Sulianti Saroso Infectious Diseases Hospital Jakarta. Indones J Infect Dis. 2017;23–7.
31. Fida A. Angka kejadian pneumonia pada pasien sepsis di ICU RSUP Dr. Kariadi Semarang. Universitas Diponegoro; 2014.
32. Breijyeh Z, Jubeh B, Karaman R. Resistance of gram-negative bacteria to current antibacterial agents and appoaches to resolve it. Molecules. 2023;28(2).
33. Pratiwi AD, Rusli M, Utomo B. Correlation between ESBL-producing bacteria infection with sepsis severity of patient in medical ward of internal medicine department Dr. Soetomo General Hospital in 2016. JUXTA J Ilm Mhs Kedokt Univ Airlangga. 2019;10(2):84.
34. Al-Sunaidar KA, Aziz NA, Hassan Y, Jamshed S, Sekar M. Association of multidrug resistance bacteria and clinical outcomes of adult patients with sepsis in the intensive care unit. Trop Med Infect Dis. 2022;7(11):1–15.
35. Raniputri KA, Harsini H, Harsini H, Reviono R, Reviono R, Saptawati L, et al. Correlation of antibiotic resistance with sepsis incidence, hospital mortality, and time of sepsis onset in community acquired bacterial pneumonia. J Respirologi Indones. 2022;42(3):185–91.
36. 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(1):1–11.
37. Vélez JW, Aragon DC, Donadi EA, Carlotti APCP. Risk factors for mortality from sepsis in an intensive care unit in Ecuador a prospective study. Med (United States). 2022;101(11):1–7.
38. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247.
39. Mohamed AKS, Mehta AA, James P. Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit. Lung India.

2018;35(1):41–6.
40. Lindström AC, Eriksson M, Mårtensson J, Oldner A, Larsson E. Nationwide case–control study of risk factors and outcomes for community-acquired sepsis. Sci Rep. 2021;11(1):1–9.
41. Li M, Huang P, Xu W, Zhou Z, Xie Y, Chen C, et al. Risk factors and a prediction model for sepsis: A multicenter retrospective study in China. J Intensive Med. 2022;2(3):183–8.