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Different Sepsis Patient Outcomes Due to Multidrug-Resistant Organisms (MDRO): A Study of Empirical Antibiotic Sensitivity Test Results

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Abstract

Background: Sepsis, a severe immune response to infection, has a concerning global mortality rate of 85%, predominantly due to Gram-negative bacteria. The rise of antibiotic resistance in these organisms complicates treatment, leading to higher mortality and prolonged hospital stays. Effective empirical antibiotics can mitigate these outcomes. **Objective:** This study compares outcomes of sepsis patients infected with multidrug-resistant organisms (MDRO) based on empirical antibiotic sensitivity testing, focusing on mortality and length of stay (LOS) within 14 days of sepsis onset. **Methods:** A prospective cohort observational study at Dr. M. Djamil General Hospital included 94 participants. Patients who died within 14 days were excluded from the LOS analysis to prevent bias. Initial assessments included culture sampling and organ dysfunction. **Results:** The study revealed no significant difference in mortality based on antibiotic sensitivity (p=0.283), but the LOS was significantly shorter in those treated with sensitive antibiotics (p<0.016). **Conclusion:** LOS was significantly affected by antibiotic sensitivity, with patients receiving effective antibiotics experiencing shorter stays, though mortality differences were not statistically significant in the 14-day window..

Keywords: *multidrug-resistant organism, empiric antibiotic, sepsis*

Introduction

Sepsis is a clinical syndrome involving immune system dysregulation, inflammation, and coagulation in response to infection. Early sepsis presents as systemic inflammatory response syndrome and may progress to septic shock, multiorgan failure, and death[1]. In 2017, the global burden of sepsis was significant, with an estimated 48.9 million cases and 11 million sepsis-related deaths, representing nearly 20% of all global deaths. According to the Global Burden of Diseases, Injuries, and Risk Factors Study, the global incidence of sepsis was around 677.5 cases per 100,000 population[2].

Sepsis is primarily caused by Gram-negative bacteria, associated with a higher mortality rate. A recent study revealed that sepsis caused by Gram-negative bacteria results in higher serum inflammatory factor concentrations and increased disease severity compared to sepsis caused by Gram-positive bacteria[3].The primary sources of Gram-negative bacterial infections are respiratory tract infections, bloodstream infections, abdominal infections, urinary tract infections, and skin infections. Antibiotic resistance among these bacteria is rising globally, leading to a serious crisis. The outer membrane of Gram-negative bacteria is key to their

resistance against various antibiotics, including β-lactams, quinolones, and colistin. In contrast, Gram-positive bacteria lack this membrane, making them less resistant to antibiotics[4].

The widespread use of antibiotics and inappropriate prescriptions are major contributors to antibiotic resistance. This issue significantly affects patient morbidity and mortality while increasing healthcare costs. Antibiotic resistance leads to the rise of multidrug-resistant organisms (MDRO), which are resistant to multiple classes of antibiotics. In 2024, the World Health Organization prioritized extended-spectrum β-lactamases-producing *Enterobacteriaceae* (ESBL-E), carbapenemase-resistant *Enterobacteriaceae* (CRE), and carbapenem-resistance *Acinetobacter baumannii* (CRAB) as critical global pathogens due to limited treatment options and high transmissibility[5].

The resistance of *Enterobacteriaceae* to third-generation cephalosporins exceeds 10% and to carbapenems is 2-7%, mainly due to the rapid spread of ESBL-producing strains. While, *Pseudomonas aeruginosa* and *A. baumannii* exhibit carbapenem resistance rates ranging from 20-40% and 40-70% in ICU-acquired infections, respectively[4]. In 2021, Dr. M. Djamil General Hospital Padang reported 2238 MDRO specimens, with *Klebsiella pneumoniae*-producing ESBL (Kp-ESBL) as the most causative bacteria, accounting for 12.2% of the specimens, followed by *Escherichia coli*-producing ESBL (Eco-ESBL) with 8.6%, CRAB with 7.4%, carbapenem-resistant *E. coli* (CREC) with 1.4%, and carbapenem-resistant *K. pneumoniae* (CRKP) with 3.6%[6].

The global burden of drug-resistant infections in 2019 was estimated at 4.95 million deaths. Of these, 1.27 million deaths were directly attributable to drug resistance. Resistance to first-line antibiotics for serious infections, such as carbapenems, cephalosporins, and penicillins, causes over 70% of deaths from all antibiotic-resistant pathogens, limiting the choice of empiric antibiotics[7]. MDRO infections not only contribute to mortality but also extend hospital stays compared to infections from antibiotic-sensitive pathogens[8].

A retrospective study by Chen *et al*. found that patients infected with MDRO had a significantly longer length of stay (LOS) compared to those without MDRO infection (β=0.55; 95% confidence interval (CI):0.02–1.09)[8]. A 2023 meta-analysis on mortality also indicated that the unadjusted case fatality rate linked to MDRO was 45.0%, with a higher adjusted lethality observed in MDRO infected individuals compared to those infected with other pathogens (adjusted odds ratio (aOR)=1.93; 95% CI:1.58-2.37). The study also emphasized a higher lethality rate in patients who did not receive appropriate empirical treatment (OR=2.27; 95% CI:1.44-3.56)[9].

Resistance to first-line antibiotics limits empirical antibiotic choices. The antibiotic of choice for ESBL infections is a combination of beta-lactam with classic beta-lactamase inhibitors such as clavulanic acid, tazobactam, or sulbactam[10]. In addition, carbapenem antibiotics (meropenem, imipenem, ertapenem) and fluoroquinolone (levofloxacin, ciprofloxacin) can also be given. The antibiotics of choice for CRE pathogen infections include ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam[11].

Early and comprehensive empirical therapy is vital for lowering mortality in severe sepsis and septic shock. The 2021 Surviving Sepsis Campaign (SCC) guidelines recommend administering intravenous empirical antibiotics within one hour of collecting blood cultures. This approach focuses on using broad-spectrum antibiotics and timely de-escalation strategies. De-escalation should consider microbiological findings, the patient's clinical status, and the

availability of suitable medications. Standard antibiotic therapy is based on the principles of Empirical Therapy. Evaluating the appropriateness of antibiotic use involves five key factors: correct dose, correct indication, correct patient, correct route, and correct duration. This assessment is a widely accepted tool for measuring antibiotic use quality in various countries[12,13].

Empirical antibiotic treatment not aligned with sensitivity test results significantly influences short-term mortality in patients suffering from severe sepsis and septic shock caused by Gram-negative bacteria. A study by Zilberberg *et al.* revealed that mortality rates increased when antibiotics did not match sensitivity results, with an odds ratio of 3.8[14].

The urgency of this research stems from the rising rates of MDRO. These organisms make it harder to treat severe sepsis and septic shock. As antibiotic resistance grows worldwide, clinicians are challenged to find effective empiric therapies. Current clinical guidelines often lack solid, evidence-based recommendations for treating sepsis linked to MDRO. Thus, it's essential to find better strategies for initial antibiotic use.

This study stands out by focusing on aligning empirical antibiotic treatment with sensitivity testing results in MDRO cases. While some research has tackled sepsis treatment and resistance, few have examined the effects of mismatches in empiric therapy due to MDRO. This is especially relevant for patient mortality and length of stay. By addressing this gap, this research aims to influence clinical practices, optimize antibiotic usage, and enhance patient outcomes in the critical early phases of sepsis.

Materials and Methods

Study Design

The study employed a prospective cohort design using an unpaired analytical observational approach at Dr. M. Djamil General Hospital, focusing on sepsis patients. In a study on sepsis, a consecutive sampling technique was used to recruit subjects and collect culture examination results from all sepsis patients treated in the inpatient installation of Internal Medicine and other wards treated together with the Tropical Infectious Diseases Division over duration of six months, from January 2024 to July 2024.

Sample

The study samples comprised research participants who met the inclusion criteria of sepsis patients with the sequential organ failure assessment (SOFA) score ≥ 2, age above 18 years, and MDRO bacterial culture results. The samples were excluded due to culture results showed no bacteria and the patient went home at his own request.

Data Collection Techniques

Case diagnosis

Sepsis patients at Dr. M. Djamil Padang General Hospital are defined by a SOFA score of ≥ 2 and an identifiable infection source. The SOFA score assesses organ dysfunction (respiratory, cardiovascular, coagulation, liver, kidney, consciousness) and is calculated on the first day of sepsis, with possible scores ranging from 2 to 24.

Eligible sepsis patients are included in the study after obtaining consent from their families. Basic data is collected, encompassing name, age, gender, comorbidities, infection source, laboratory findings, and empirical antibiotics administered. Additionally, prognostic factors for mortality, such as the acute physiology, age and chronic health evaluation (APACHE) II score, are documented. This score evaluates mortality risk based on physiological parameters (consciousness, MAP, heart rate, respiratory rate, temperature, oxygen requirement, arterial pH, serum bicarbonate, serum sodium and potassium, creatinine, hematocrit, leukocytes),

age, and prior organ dysfunction, also measured on the first day of sepsis, with scores ranging from 0 to 71.

The study also tracks the use of vasopressors and medical devices like ventilators. Vasopressor use, defined as the administration of medications (norepinephrine, epinephrine, dobutamine, vasopressin) to maintain MAP above 65 mmHg, and ventilator use, indicating mechanical ventilation necessity for oxygen saturation above 90%, are recorded.

Collection of blood

Blood culture examination is carried out by taking venous blood from 2 different sides of the body using a 10 cc syringe, then the blood taken is put into 2 BacT/ALERT blood culture media tubes. While in taking urine culture, urine aspiration is carried out using a 10cc syringe through a urinary catheter while observing aseptic measures. Likewise, in taking sputum culture using a mucus extractor to be able to take secretions/sputum which are stored in a sterile sputum container while always observing aseptic measures. For taking samples of other infection focuses such as pus specimens, it is carried out on patients with purulent wounds or ulcers, infected surgical wounds, by swabbing the wound without touching the edges of the wound, swabs on the wounds obtained are stored in a sterile container while always observing aseptic measures. All blood, urine, sputum and pus culture specimens are sent to the Microbiology Laboratory of Dr. M. Djamil General Hospital Padang for culture examination

ESBL-E and CRO isolates detection

Detection of ESBL-E and carbapenem resistant organisms (CRO) can be performed using phenotype-based tests with the VITEK-2 system. This automated microbiology platform employs growth-based technology and comes in three variations: VITEK-2 compact, VITEK-2, and VITEK-2XL. Each version has different levels of capacity and automation. All are equipped with colorimetric reagent cards that undergo automatic incubation and interpretation[15]. In this study, we used VITEK-2 compact to identified ESBL-E and CRO in the microbiology laboratory at Dr. M. Djamil General Hospital, Padang.

Empirical antibiotics and sensitivity testing

Empirical antibiotics are broad-spectrum medications given to patients diagnosed with sepsis before sensitivity test results and microorganism identification are available. Empirical antibiotic sensitivity testing evaluates the effectiveness of these antibiotics against cultured microorganisms. The VITEK-2 Compact is currently employed for this purpose. This device uses advanced colorimetry and turbidimetry to identify microorganisms and assess antimicrobial sensitivity, completing the process within 5 to 8 hours. This rapid identification benefits both hospitals and patients by allowing for quicker treatment initiation[16]. In this study, we utilized the microorganism phenotype test method with the VITEK-2 Compact in the microbiology lab at Dr. M. Djamil General Hospital. The examination results indicate whether the microorganisms are sensitive or resistant.

Data Analysis Techniques

The study analyzed independent and dependent variables, focusing on empirical antibiotic sensitivity test results at sepsis diagnosis as the independent variable and mortality within 14 days of sepsis onset and length of stay (LOS) as the dependent variables. Mortality was defined as survival or death within 14 days, while LOS was calculated as the total days from sepsis diagnosis to hospital discharge. Patient characteristics and treatment outcomes were examined using univariate and bivariate analyses. Univariate analysis summarized characteristics as numbers and percentages, with a normality test performed on the LOS

variable. Bivariate analysis used the Chi-Square test to assess the relationship between antibiotic sensitivity and mortality, and the Mann-Whitney test for the non-normally distributed LOS variable. Data analysis was conducted with SPSS Statistics software, version.

Ethical Consideration

This study received ethical approval from the Institutional Review Board (IRB) of Dr. M. Djamil General Hospital, Padang (Approval No. DP.04.03/D.XVI.XI/541/2023). We adhered to the World Medical Association's Code of Ethics (Declaration of Helsinki) for research involving human subjects. Informed consent was obtained, and data were sourced from medical records. All medical information will be kept confidential.

Result

In the study, 49 women (52.1%) and 45 men (47.9%) were sepsis patients. Gender did not show a significant relationship with mortality (p=0.233). The mean age of sepsis patients who survived was 52.98 (SD ± 14.70), versus those who died within 14 days of sepsis onset was 58.06 (SD ± 14.9) with a p-value of 0.113. The median SOFA score of sepsis patients who survived versus those who died was 7 (3-13) versus 7.5 (4-13) with p=0.709. The mean APACHE score in sepsis patients who survived versus those who died was 19.93 (SD ± 6.69) versus 20.79 (SD ± 5.37) with p=0.523. The most prevalent comorbidity was diabetes mellitus, affecting 24 patients (25.5%), followed by cerebrovascular disease in 21 patients (22.3%) and malignancy in 20 patients (21.3%). There was no significant correlation between comorbidity and hospital mortality (p>0.05).

The primary focus of infection was the lungs in 67 patients (71.3%), followed by skin soft tissue in 18 patients (19.1%) and the urinary tract in 9 patients (9.6%). The predominant microorganisms identified were *K. pneumoniae* with 44 isolates (46.7%), *A. baumannii* with 20 isolates (21.3%), *E. coli* with 19 isolates (20.2%), and *P. aeruginosa* with 4 isolates (4.2%). In sepsis patients, the most commonly used empirical antibiotic combinations were ampicillin sulbactam and levofloxacin (27.7%), followed by cefepime and amikacin (23.4%), cefepime and levofloxacin (18.1%), and meropenem and amikacin (12.8%).

The use of vasopressors is a factor associated with mortality. Mortality in patients using vasopressors was 20 patients (58.8%) compared to 14 patients (41.2%) who did not use vasopressors (p=0.019). The use of ventilators was not associated with in-hospital mortality (p=0.156) presented in (Table 1).

The prevalent MDRO pathogens in lung infections are *K. pneumoniae*, *A. baumannii*, and *E. coli*. In skin and soft tissue infections, the same pathogens are noted, along with *E. coli*. For urinary tract infections, *K. pneumoniae* and *E. coli* are commonly found. The distribution of MDRO pathogens based on the focus of infection is detailed in (Table 2). ESBL and carbapenemase-producing pathogens were found in 50 patients (53.2%) and 44 patients (46.8%) out of a total of 94 patients, respectively. The distribution of pathogens based on MDRO classification is illustrated in (Figure 1).

This study reveals that meropenem exhibited the highest sensitivity among antibiotic groups, showing 100% effectiveness against 50 ESBL-producing culture isolates. Amikacin followed closely, being effective for 48 isolates (96%). In contrast, cefepime, gentamicin, and trimethoprim-sulfamethoxazole demonstrated much lower sensitivities of 50%, 46%, and 30%, respectively. The sensitivity rates for ceftazidime, ampicillin sulbactam, ciprofloxacin, and ceftriaxone were notably poor, at 10%, 6%, 6%, and 0%. For

carbapenemase-producing pathogens, amikacin showed a relatively good sensitivity, effective against 31 out of 44 isolates (77.3%), while trimethoprim-sulfamethoxazole's sensitivity was poor at 43.2% are shown in (Table 3).

Table 1. Characteristics of Research Subjects

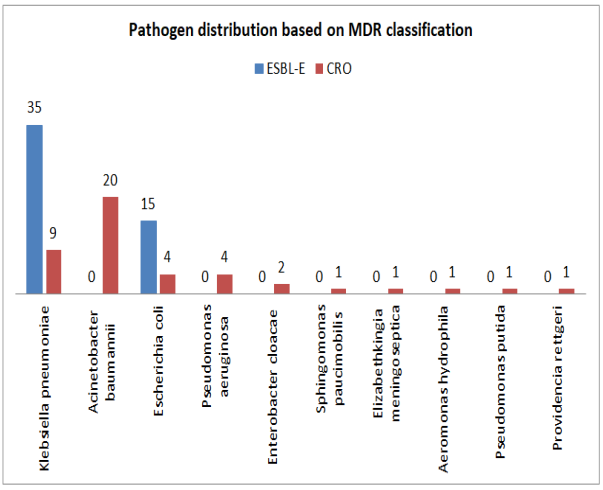
Variables	n = 94	Survival 14 days of sepsis onset		p
		Survived f=60 (%)	Died f=34 (%)	
Gender				0.233
Male	45 (47.9)	32(53.3)	13(38.2)	
Female	49 (52.1)	28(46.7)	21 (61.8)	
Age (Mean)		52.98 ± 14.7	58.06 ± 14.9	0.113
18-39 years	17 (18.1)	12(20)	5(14.7)	
40-59 years	37 (39.4)	27(45)	10 (29.4)	
≥ 60 years	40 (42.5)	21(35)	19 (55.9)	
SOFA score (Median)		7(3-13)	7.5(4-13)	0.709
APACHE II score (Mean)		19.93 ± 6.69	20.79 ± 5.37	0.523
Comorbidities				
Diabetes Mellitus	24 (25.5)	13(21.7)	11 (32.4)	0.37
Cerebrovascular Disease	21 (22.3)	13(21.7)	8(23.5)	1.00
Malignancy	20 (21.3)	12(0.2)	8(23.5)	0.88
Cardiovascular Disease	10 (10.6)	8(8.5)	2(5.9)	
Chronic Kidney Disease	9(9.5)	6(10)	3(8.8)	
Chronic Lung Disease	8 (8.5)	5 (8.3)	3 (8.8)	
Chronic Liver Disease	5 (5.3)	4 (6.7)	1 (2.9)	
Aplastic Anemia	2 (2.1)	1 (1.7)	1 (2.9)	
Immunodeficiency	1 (1.1)	1 (1.7)	0	
No comorbidities	16 (17)	11(18.3)	5(14.7)	
Focus of Infection				
Lung	67 (71.3)	44(73.3)	23 (67.6)	
Skin Soft Tissue	18 (19.1)	11(18.4)	7(20.6)	
Urinary Tract	9 (9.6)	5 (8.3)	4 (11.8)	
Microorganisms				
Klebsiella pneumoniae	44 (46.7)	28(46.6)	16 (47.1)	
Acinetobacter baumannii	20 (21.3)	9(15)	11 (32.4)	
Escherichia coli	19 (20.2)	14(23.3)	5(14.7)	
Pseudomonas aeruginosa	4 (4.2)	2 (3.3)	2 (5.8)	
Enterobacter cloacae	2 (2.1)	2 (3.3)	0	
Sphingomonas paucimobilis	1 (1.1)	1 (1.7)	0	
Elizabethkingia meningoseptica	1 (1.1)	1 (1.7)	0	
Aeromonas hydrophila	1 (1.1)	1 (1.7)	0	
Pseudomonas putida	1 (1.1)	1 (1.7)	0	
Providencia rettgeri	1 (1.1)	1 (1.7)	0	
MDR Classification				
ESBL-*Enterobacteriaceae*	50 (53.2)	34(56.7)	16 (47.1)	
Carbapenem Resistant Organism	44 (46.8)	26(43.3)	18 (52.9)	
Empirical Antibiotics				
Ampicillin Sulbactam + Levofloxacin	26 (27.7)	20(33.3)	6(17.6)	
Cefepime + Amikacin	22 (23.4)	13(21.8)	9(26.5)	
Cefepime + Levofloxacin	17 (18.1)	8(13.3)	9(26.5)	
Meropenem + Amikacin	12 (12.8)	8(13.3)	411.8)	
Ceftriaxone + Levofloxacin	8 (8.5)	6 (10)	2 (5.8)	
Meropenem + Levofloxacin	6 (6.4)	2 (3.3)	4 (11.8)	
Ceftazidime + Levofloxacin	2 (2.1)	2 (3.3)	0	
Vancomycin + Amikacin	1 (1.1)	1 (1.7)	0	
Use of Vasopressors				
Yes	39 (41.5)	19(31.7)	20 (58.8)	0.019
No	55 (58.5)	41(68.3)	14 (41.2)	
Use of Ventilator				
Yes	38 (40.4)	28(46.7)	10 (29.4)	0.156
No	56 (59.6)	32(53.3)	24 (70.6)	

Source : *Primary Data, 2024*

Table 2. Distribution of MDR pathogens based on the focus of infection

Microorganisms	Focus of Infection		
	Lung n=67 f (%)	Skin Soft Tissue n=18 f (%)	Urinary Tract n=9 f (%)
Klebsiella pneumoniae	36 (53.7)	4(22.2)	4(44.4)
Acinetobacter baumannii	15 (22.4)	5(27.8)	0
Escherichia coli	11 (16.4)	5(27.8)	3(33.4)
Pseudomonas aeruginosa	1 (1.5)	2 (11.1)	1 (11.1)
Enterobacter cloacae	2 (3)	0	0
Sphingomonas paucimobilis	1 (1.5)	0	0
Elizabethkingia meningoseptica	0	1 (5.5)	0
Aeromonas hydrophila	1 (1.5)	0	0
Pseudomonas putida	0	0	1 (11.1)
Providencia rettgeri	0	1 (5.5)	0

Source : *Primary Data, 2024*



Source : *Primary Data, 2024*

Figure 1. Pathogen distribution based on MDR classification

Differences in 14-day mortality outcomes based on empirical antibiotic sensitivity testing

A Chi Square test was performed to evaluate the relationship between empirical antibiotic sensitivity results and sepsis patient outcomes within 14 days. The data showed that 33 patients (70.2%) with sensitive antibiotic results survived, while 14 patients (29.8%) died. Conversely, among those with resistant results, 27 patients (57.4%) survived and 20 patients (42.6%) died. The statistical analysis yielded a p-value of 0.283, indicating no statistically significant difference in outcomes relative to antibiotic sensitivity. Nonetheless, the clinical relevance remains, as the survival rates among patients with sensitive antibiotics differed by over 40%, in line with the minimum sample size formula are shown in (Table 4).

Table 3. Empirical antibiotic sensitivity to MDR pathogens

Antibiotic	Number of ESBL-E Isolates n=50 f (%)	Number of CRO Isolates n=44 f (%)
Betalactams + Betalactamase Inhibitors		
Ampicillin sulbactam	3 (6)	1 (2.2)
Cephalosporins		
Ceftriaxone	0 (0)	0 (0)
Ceftazidime	5 (10)	1 (2.2)
Cefepime	25 (50)	0 (0)
Carbapanems		
Meropenem	50 (100)	0 (0)
Quinolones		
Ciprofloxacin	3 (6)	0 (0)
Aminoglycosides		
Amikacin	48 (96)	31 (77.3)
Gentamicin	23 (46)	3 (6.8)
Others		
Trimethoprim-sulfamethoxazole	15 (30)	19 (43.2)

Source : *Primary Data, 2024*

Table 4. The relationship between empirical antibiotic sensitivity test results and sepsis patient mortality within 14 days

Empirical Antibiotic Sensitivity Test Results	Patient Outcomes within 14 days of sepsis onset				p
	Survived		Died		
	f	%	f	%	
Sensitive (n=47)	33	70.2	14	29.8	0.283
Resistant (n=47)	27	57.4	20	42.6	
Total	60	63.8	34	36.2	

Source : *Primary Data, 2024*

Table 5. The difference in length of stay based on the results of the antibiotic sensitivity test

Empirical Antibiotic Sensitivity Test Results	Median Length of Stay (Days) (Minimum-Maximum)	p
Sensitive (n=27)	13 (6-20)	0.016
Resistant (n=27)	15 (13-25)	

Source : *Primary Data, 2024*

Differences in LOS based on empirical antibiotic sensitivity testing

Based on the antibiotic sensitivity testing, the study excluded patients who died within 14 days of sepsis onset to avoid bias. The analysis focused on 54 living patients out of 94 sepsis patients. The LOS had a non-normal distribution, even after data transformation using the log10 feature. A non-parametric test showed a statistically significant difference in the results of the antibiotic sensitivity test. The difference in LOS was statistically significant with a p-value of 0.016, but not clinically significant due to a small difference in median LOS (2 days) compared to the difference in mean LOS (8 days) are shown in (Table 5).

Discussion

The study revealed that the highest population of sepsis cases occurred in individuals over 60 years old, accounting for 42.5% of the cases. The proportion of deaths also increased with age: 14.7% for 18-39 years, 29.4% for 40-59 years, and 55.9% for over 60 years. In a study by Martin-Loeches *et al*. it was found that sepsis patients were predominantly over 65 years old[17]. Older individuals are highly vulnerable to sepsis due to existing comorbidities, weakened immune function, sarcopenia, decreased physiological reserves linked to aging, malnutrition, and polypharmacy. Elderly patients tend to develop medical complications during hospitalization, leading to significant adverse effects such as high mortality rates and prolonged LOS[18].

The study revealed a higher mortality rate in women (61.8%) compared to men (38.2%). Meanwhile, a recent cohort study found different results, women had lower 30-day mortality (10.1% vs. 13.6%; p=0.016) and in-hospital mortality (8.0% vs. 11.1%; p=0.02) compared to men. However, the multivariable analysis revealed that patient sex was not an independent predictor of 30-day mortality[19]. Evidence suggests that sex influences the host response to sepsis, with women showing a protective effect. Women demonstrate faster clearance of bacteria and a less reactive inflammatory response compared to men. Estrogens promote efficient immune responses, while androgens have a suppressive effect[20].

SOFA and APACHE II scores have been widely used in predicting in-hospital mortality. This study found that the mean SOFA score in the group of patients who survived and died within 14 days of sepsis onset was 7 (3-13) and 7.5 (4-13) respectively (p=0.233). Meanwhile, the mean APACHE II score in the group of survivors and died within 14 days of sepsis onset was 20.84 (SD±7.7) and 21.23 (SD±5.3) respectively (p=0.059). A cross-sectional study by Oliveira-Maia *et al*.[21] found an increase in SOFA and APACHE II scores in the group of patients who died during hospitalization compared to survived patients. The group of patients who died showed a mean SOFA score of 5 (3-7) and a mean APACHE II of 22.8 (SD±7.2), compared to the group of patients who survived with a mean SOFA score of 2 (2-3.8) and a mean APACHE II of 14.1 (SD±6.7).

In this study, the most prevalent comorbidities were diabetes mellitus (25.5%), stroke (22.3%), and solid tumors (20.2%). Another study at the same center found different results: chronic kidney disease (28%), diabetes mellitus (19.2%), malignancy (12.4%), and stroke (10.2%) were the most common comorbidities. Diabetes mellitus is a common metabolic disease around the globe. It is linked to a higher risk of infections. This condition disrupts the body's defense mechanisms, making patients more susceptible to infections. Individuals with diabetes face a greater chance of infection and sepsis due to elevated blood glucose levels and changes in immune response. Both the innate and adaptive immune systems are affected, leading to chronic inflammation, immune suppression, and increased complications from infections, especially in cases of type 2 diabetes.

Additionally, the activation of toll-like receptors 2 (TLR2) and toll-like receptor 4 (TLR4) amplifies the inflammatory response associated with diabetes[22,23,24].

Nosocomial infections, such as hospital-acquired pneumonia (HAP) and urinary tract infections, are common in patients with cerebrovascular diseases like acute stroke. Ventilator-associated pneumonia (VAP) is an infection of the lung parenchyma that occurs after 48 hours of tracheal intubation and mechanical ventilation. In the Intensive Care Unit (ICU), VAP is the most frequent nosocomial infection, affecting 20–36% of critically ill patients. Late-onset VAP is more likely caused by MDRO and is associated with higher morbidity and mortality. In ventilated patients, the body's natural defense system is disrupted, leading to the rapid development of pathogenic bacteria colonies like *Pseudomonas*, *Acinetobacter*, and Methicillin-resistant *Staphylococcus aureus* (MRSA) within 24 hours of ICU admission[25].

Immunosuppression related to cancer treatments heightens the risk of infections and sepsis. Chemotherapy and radiotherapy compromise the phagocytic function of neutrophils and monocytes, reducing their numbers and impairing their ability to respond to infections. The likelihood of infection and sepsis correlates strongly with the severity and duration of neutropenia and monocytopenia. Cytotoxic treatments can disrupt lymphocyte and NK cell functions, while other therapies like anti-lymphoproliferative agents and monoclonal antibodies—such as fludarabine, bendamustine, ibrutinib, rituximab, and alemtuzumab—can lead to B- and T-cell lymphopenia. Additionally, corticosteroids, frequently used in cancer care, further enhance immunosuppression[26].

The study found that sepsis infections mostly occurred in the respiratory tract (71.3%), skin and soft tissue (19.1%), and urinary tract (9.6%). Wang *et al*.[27] discovered in 2020 that the most common sites of infection were the lungs (55.5%), intra-abdominal infection (24.4%), pleura (5.8%), and skin soft tissue (5.1%). The lungs are particularly susceptible during sepsis. Managing sepsis in patients with lung infections is more challenging and correlates with higher mortality rates. This occurs because sepsis triggers systemic organ damage through inflammatory responses. Factors such as leukocyte leakage, coagulation issues, and inflammation-driven capillary dilation contribute to severe tissue edema. As sepsis advances, the collapse of pulmonary capillaries results in substantial leakage of protein-rich fluid into the lung interstitium[28].

ESBL-producing pathogens accounted for 53.2% of MDRO classifications, while carbapenemase-producing pathogens made up 46.8%. Fadrian *et al*.[22] study at Dr. M Djamil General Hospital also revealed that *K. pneumonia* (27.7%), *E. coli* (26.5%), and *A. baumannii* (13.3%) were the primary Gram-negative pathogens causing sepsis. ESBL-producing pathogens and carbapenemase-producing pathogens are accounted for 43.5% and 12.1%, respectively.

ESBL and carbapenemase-producing pathogens are widespread and contribute significantly to antibiotic resistance. The overuse of carbapenem antibiotics in treating ESBL-producing pathogen infections has resulted in high carbapenemase resistance. Carbapenems play a critical role in managing severely ill patients or those with Gram-negative bacterial infections that are resistant to the majority of antibiotics. Resistance to carbapenems is most prevalent in *Enterobacteriaceae* bacteria, including *K. pneumonia* and *E. coli*, which are accountable for infection and antibiotic resistance[29].

ESBL are enzymes that hydrolyze antibiotics, particularly those from the penicillin group and various generations of cephalosporins, including aztreonam. They

inactivate these antibiotics by breaking chemical bonds through hydrolysis, especially targeting amide and ester compounds[8]. CRO include bacteria either inherently resistant to carbapenems or those harboring mobile genetic elements (MGE), like plasmids, that produce carbapenemase enzymes. MGE facilitate the transfer of resistance traits among bacteria[30].

Carbapenem resistance primarily arises from two mechanisms: the production of carbapenemases, which are enzymes capable of hydrolyzing a wide range of β-lactams, and the activity of β-lactamases combined with structural mutations (such as those seen in ESBL and AmpC cephalosporinase). Resistance can also result from impaired antibiotic access to the active site due to reduced porin expression in the outer membrane of Gram-negative bacteria. *P. aeruginosa* exemplifies this, as its reduced porin expression contributes to its intrinsic antibiotic resistance[31,32].

The ESKAPE pathogen is known for antibiotic resistance. It primarily comprises Gram-negative bacteria. ESBL-E are the most common among all MDRO. Eco-ESBL and Kp-ESBL make up 35% of all *E. coli* and *K. pneumoniae* isolates. Sepsis resulting from ESBL-E is linked to higher mortality compared to sepsis caused by non-ESBL-E[33]. Gram-negative bacteria frequently cause nosocomial infections in hospitals. Sepsis caused by Gram-negative bacteria exhibits elevated levels of inflammatory biomarkers such as C-reactive protein, procalcitonin, and proinflammatory cytokines, including tumor necrosis factor-α, interferon-γ, and interleukins, compared to sepsis caused by Gram-positive bacteria[34].

Timely and appropriate initiation of antibiotic therapy in sepsis is crucial. Clinicians must navigate the complexities of varied infection sites and disease severity to choose the correct empiric regimen. Empirical treatment should focus on the most prevalent pathogens associated with sepsis in specific patient groups. Antibiotics considered appropriate are those to which the causative pathogens show in vitro susceptibility or those suitable for the suspected infection site in cases of culture-negative sepsis. Selecting the right empiric antibiotic correlates with improved outcomes in sepsis and septic shock patients. The SSC 2021 recommends broad-spectrum empiric therapy with one or multiple antimicrobials to address all probable pathogens, including bacteria andpotential fungal or viral agents[12,35].

In this study, the most frequently used empirical antibiotic combinations were ampicillin sulbactam and levofloxacin (27.7%). This choice aligns with the prevalent infection site in sepsis patients, specifically the lungs. The approach is consistent with the Infectious Disease Society of America (IDSA) guidelines, which recommend empirical therapy based on infection site and the host's immune status. For community-acquired pulmonary (CAP) infections, empirical therapy can include regimens combining a beta-lactam (ampicillin + sulbactam, ceftriaxone, or ceftaroline) with a macrolide (azithromycin or clarithromycin), or with a respiratory fluoroquinolone (levofloxacin or moxifloxacin)[36].

The study revealed that the use of vasopressors is a significant risk factor for mortality in sepsis patients (p=0.019). Septic shock, characterized by persistent hypotension and organ dysfunction despite adequate fluid therapy, is associated with a global mortality rate increase of up to 60%. Vasopressors, particularly catecholamine or non-catecholamine vasopressors, are an appropriate strategy for increasing vascular tone. Early administration of vasopressors in septic shock is shown to improve hemodynamics and patient life expectancy[37].

Research by Ospina *et al.* demonstrated a higher risk of mortality in patients who experienced delayed vasopressor administration compared to those who received

vasopressors very early[37] The risk of mortality in patients with septic shock is also closely related to the dose of vasopressors used. Research by Xu *et al.* discovered that low doses of *norepinephrine (*NE) were linked to a decrease in 28-day mortality (OR=0.660; 95% CI:0.518–0.840; p<0.001) compared to patients in the high doses of NE group[38].

Differences in mortality outcomes based on empirical antibiotic sensitivity test results

The study found no significant difference in mortality outcomes between patients receiving sensitive and resistant empirical antibiotics based on antibiotic sensitivity test results. This statistically insignificant result could simply be due to our limitation with the small number of patients in this study. However, we believe that these results are of clinical significance and should not be overlooked. However, mortality rates were higher in patients receiving resistant antibiotics. The findings align with the Luengarun *et al*.[39] study, which showed that patients with resistant empirical antibiotic therapy had a higher mortality rate compared to those with sensitive empirical antibiotic therapy. Administering resistant antibiotics within 24 hours of sepsis onset reduced survival rates compared to sensitive antibiotics. The use of resistant antibiotics increased the risk of death by 2.52 times. Administration of resistant antibiotics will result in failure to eradicate pathogens so that the inflammatory process will continue. Other factors affecting mortality include the timing of antibiotic administration since the onset of sepsis, septic shock, congestive heart failure, age over 65 years, APACHE score above 25, thrombocytopenia, and hypoalbumin.

In our study, we observed a notable difference in survival rates between patients responsive to empirical antibiotic therapy (70.2%) and those resistant (57.4%). Similarly, Ti'cac *et al.*[40] found that patients receiving appropriate empirical therapy for sepsis demonstrated improved clinical outcomes, with 52.8% showing enhanced responses by day 7, compared to 47.4% in the inadequately treated group. These findings underscore the impact of effective antibiotic therapy on survival in sepsis patients.

Assessing pre-existing comorbidities is crucial for predicting mortality outcomes in sepsis, as underlying chronic conditions can significantly influence patient outcomes. In both the Luengarun *et al*. study and our study, diabetes mellitus is the most common comorbidity among patients. Diabetes significantly affects sepsis patient outcomes as a comorbid risk factor. Diabetic patients in sepsis conditions often experience acute renal failure complications, with a high incidence of 27% to 73%. Reactive oxygen species (ROS) and inflammatory mediators lead to glycocalyx damage, affecting microcirculation and causing organ damage. Severe diabetes and sepsis also lead to erythrocyte hemolysis, worsening microcirculation and accelerating organ dysfunction[39,41].

The study collected culture samples from the infection site, while Luengarun *et al*. obtained blood culture samples to identify sepsis-causing bacteria. The presence of microorganisms in the blood culture confirms bacteremia as the infection source. Culture samples from the infection site, such as sputum, urine, or wound bed swabs in skin infections, are heavily influenced by bacterial colonies at that location. Therefore, the microorganisms identified in the culture may not necessarily be the primary cause of the infection in this study. This finding may explain the relatively high survival rate of patients receiving antibiotics resistant to MDRO bacteria[39,42].

Several studies have shown that APACHE II and SOFA scores can predict patient prognosis in sepsis. Various scoring systems have been developed over the last three decades to assess illness severity and in-

hospital mortality in critically ill patients. APACHE and SOFA scores predict in-hospital mortality based on physiological status and organ dysfunction. Sepsis can cause vascular dysfunction, cardiac dysfunction, and cellular dysfunction leading to anaerobic metabolism and lactate production. High lactate levels (>2 mmol/L) are linked to a higher risk of death in sepsis patients, regardless of hemodynamic status[43].

Hemodynamic management significantly impacts sepsis patient outcomes. Early goal-directed therapy (EGDT) focuses on aggressive fluid resuscitation, vasopressor administration, and blood transfusion to achieve specific hemodynamic targets. More IV fluids in EGDT have biological effects that improve tissue perfusion, prevent organ damage, and increase survival chances in sepsis patients. The EGDT algorithm targets central venous pressure of 8–12 mmHg (with fluid administration), mean arterial pressure (MAP) of 65–90 mmHg (with vasoactive agents), and central venous oxygen saturation (ScvO2) ≥70%. Regular assessment of hemodynamic status is crucial to optimize tissue perfusion in sepsis and septic shock patients[44].

Fluid administration post-initial resuscitation should be individualized based on the patient's fluid response. It's essential to monitor tissue perfusion and assess the benefits and risks of fluid infusion to prevent tissue edema from exacerbating organ dysfunction. Research by Shapiro *et al.* suggests that while restrictive fluid therapy (prioritizing vasopressors and lower intravenous fluid volumes) is not better than liberal fluid therapy (prioritizing higher intravenous fluid volumes before using vasopressors), it can reduce the risk of tissue edema[45].

Sepsis is a life-threatening condition caused by the body's exaggerated response to an infection. This response triggers the release of excessive proinflammatory cytokines, leading to a severe and persistent inflammatory reaction known as a "cytokine storm". The heightened inflammatory response in septic shock is linked to high mortality rates and the production of pro-inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) β and interferon- gamma (IFN- γ) are known to drive the hyperinflammatory response to infection[46].

Sepsis disrupts the production of crucial hormones such as cortisol, which possesses anti-inflammatory properties. Abnormal cortisol levels in the blood are associated with sepsis. Initially, cortisol levels increase as a result of heightened secretion from the adrenal glands. However, as the disease progresses, cortisol levels may drop due to impaired adrenal function, resulting in relative adrenal insufficiency. The term critical-illness-related corticosteroid insufficiency (CIRCI) was introduced to describe a condition where corticosteroid cellular activity is inadequate for the severity of the patient's illness. CIRCI can result from decreased adrenal steroid production or tissue resistance to glucocorticoids, leading to an exaggerated and prolonged proinflammatory response[47].

Critical illnesses like sepsis can lead to changes in hormone levels, affecting thyroid axis activity. Thyroid hormone is crucial for immune response, blood clotting, and cardiovascular function, providing metabolic support for vital organs like the brain and immune system. Reduced thyroid hormone production increases the risk of blood clotting disorders and heart dysfunction, potentially causing organ failure due to poor organ perfusion. Studies have reported that thyroid hormone changes in critical conditions such as sepsis are linked to increased mortality. A recent study by Siampa *et al*. showed an association between the severity of sepsis and thyroid function levels. The study found a significant association between fT3 ($p<0.001$) and fT4 ($p=0.032$) levels with the severity of sepsis[48].

Difference in LOS based on empirical antibiotic sensitivity test results

The study found a significant difference in treatment duration between patients with antibiotic sensitivity test results. The median of LOS patients with sensitive antibiotics was 2 days shorter than for those with resistant antibiotics (p=0.016). Patients who died within 14 days of sepsis onset were excluded from the analysis. Chang *et al*. study also showed that using sensitive antibiotics in sepsis conditions can decrease hospital stay. The use of targeted antibiotics in sepsis can shorten hospital stays by effectively treating infections and promoting faster recovery. Administering appropriate antibiotic therapy and supportive treatment within the first hour of sepsis onset is linked to high survival rates and shorter LOS[49, 50].

Prolonged hospital stays can lead to various adverse events, such as multidrug-resistant infections, delirium, physical decline, and emotional distress, all of which can adversely affect patient outcomes. When patients develop sepsis following extended periods in the hospital, their host responses may differ due to prolonged exposure to hospital pathogens and the reduced physiological reserves associated with pre-existing health conditions. Several factors, including disease severity, frailty, complications, socioeconomic status, and family support, can impact the duration of hospital stays in sepsis patients[51,52].

Nosocomial infections often occur due to environmental factors in the hospital setting. Estimates suggest that 10-20% of these infections arise from airborne transmission. The air within hospital environments contains a diverse array of microorganisms. These include bacteria, viruses, fungi, and parasites, all of which have the potential to cause nosocomial infections. Infections can stem from cross infections, where pathogens are transmitted from other patients, or from endogenous infections, which involve the patient's own normal flora. The prevalence and types of nosocomial infections can vary significantly from one hospital to another[53].

A study by Chen *et al.* revealed that sepsis-related hospital care accounts for 3.6% of Taiwan's national healthcare expenditure, equating to an average annual cost of 33.5 billion New Taiwan Dollar (NT dollars). This expenditure surpasses that for cancer and diabetes. However, it's essential to recognize that not all costs associated with sepsis hospitalizations are directly for sepsis treatment. The presence of comorbidities may inflate the estimated costs of sepsis. Nonetheless, the economic impact of sepsis remains significant[52].

Risk factors for MDRO infection play a crucial role in guiding clinicians to administer appropriate antibiotics. The Italian score, with a sensitivity, specificity, and accuracy above 80%, is utilized for predicting ESBL-producing bacterial infections[54]. Furthermore, genomic examination for *Enterobacteriaceae*, *A. baumannii*, *and P. aeruginosa* bacteria can detect carbapenemase-producing bacterial infections. The identification of blaNDM, blaOXA-48, blaOXA-23-like, blaIMP, and blaVIM genes in patients diagnosed with sepsis aids clinicians in determining antibiotic therapy[55].

The rational use of antibiotics should be carefully considered. The Gyssens Index offers a method to evaluate the appropriateness of antibiotics based on their quality. Fadrian *et al.* have conducted research at Dr. M. Djamil Padang General Hospital, revealing a significant link between the appropriateness of antibiotic administration and patient outcomes post-hospital discharge. The study found that inappropriate use of antibiotics (Gyssens I-IV) and the use of antibiotics without indications (Gyssens V) was associated with a 1.96 and 4.05 times increased risk of death, respectively ($p<0.05$). Furthermore, proper antibiotic

administration can enhance outcomes for sepsis patients and reduce hospital stay duration[56].

Limitations of the study

This study is limited by its small sample size, which may affect the generalizability of the findings, especially given the variability in outcomes for sepsis patients. The research focuses solely on sepsis outcomes associated with MDRO based on empirical antibiotic sensitivity tests. Key factors, such as pro-inflammatory cytokine levels and thyroid hormones, were not addressed. Additionally, the study lacks molecular data regarding the resistance mechanisms of the pathogens identified, highlighting a gap for future research. Moreover, the results may not be applicable beyond the specific hospital in Padang, Indonesia. Future research should involve multiple hospitals to provide a more comprehensive understanding of sepsis patient outcomes and their influencing factors.

Conclusion

The study at Dr. M. Djamil General Hospital found that differences in outcomes among sepsis patients were not statistically significant in terms of mortality within 14 days based on antibiotic sensitivity tests. However, the LOS showed statistical significance. Patients who received sensitive antibiotics had a shorter stay compared to those who received resistant antibiotics. Consider risk factors for MDRO infections when selecting initial antibiotics to reduce hospital stay. Future development of rapid molecular-based bacterial detection could improve patient outcomes.

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References

1. Dugar S, Choudhary C, Duggal A. Sepsis and septic shock: Guideline-based management. *Cleve Clin J Med*. 2020;87(1):53-64.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-211. doi: 10.1016/S0140-6736(19)32989-7.
3. Tang A, Shi Y, Dong Q, Wang S, Ge Y, et al. *Crit Care*. 2023;27(1):467. doi: 10.1186/s13054-023-04750-w.
4. Breijyeh Z, Jubeh B, Karaman R. Resistance of Gram-Negative Bacteria to Current Antibacterial Agents and Approaches to Resolve It. *Molecules*. 2020;25(6):1340. doi: 10.3390/molecules25061340.
5. Uyar NY, Ayaş M. Importance of Enterobacterales that Develop Resistance Due to Expanded-Spectrum Beta-Lactamase and Carbapenemase Production. *Haydarpasa Numune Med J*. 2024;64(1):111-117. doi: 10.14744/hnhj.2022.56588.
6. Fadrian F, Linosefa L. *Pocket Book of Antibiogram of Dr. M. Djamil Padang General Hospital in 2021*.; 2021.
7. Murray J, Bacci S, Hogberg LD, Kaczmarek M, Keramarou M, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399:629–55.
8. Chen YP, Tasi XW, Chang K, Cao XD, Chen JR, et al. Multi-Drug Resistant Organisms Infection Impact on Patients Length of Stay in Respiratory Care Ward. *Antibiotics (Basel)*. 2021;10(5):608. doi: 10.3390/antibiotics10050608.

9. Ciapponi A, Bardach A, Sandoval MM, Palermo MC, Navarro E, et al. Systematic Review and Meta-analysis of Deaths Attributable to Antimicrobial Resistance, Latin America. *Emerg Infect Dis.* 2023;29(11): 2335-2344. doi: 10.3201/eid2911.230753.
10. Carcione D, Siracusa C, Sulejmani A, Leoni V, Intra J. Old and New Beta-Lactamase Inhibitors: Molecular Structure, Mechanism of Action, and Clinical Use. *Antibiotics*. 2021;10(8):995. doi: 10.3390/antibiotics10080995.
11. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, et al. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P.aeruginosa). *Clin Infect Dis*. 2022;75:187–212. doi: 10.1093/cid/ciac268.
12. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y.
13. Setiadi F, Kumala S, Utami R H, Subhan A. Analisis faktor-faktor yang mempengaruhi outcome terapi pasien pneumonia di rumah sakit umum pusat Fatmawati Jakarta. *Healthy Tadulako Journal (Jurnal Kesehatan Tadulako)*. 2019;5(3):18-28.
14. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Gillamant C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. *Critical Care*. 2014;18(6):596. doi: 10.1186/s13054-014-0596-8.
15. Peacock SJ, Paterson GK. Mechanisms of Methicillin Resistance in Staphylococcus aureus. *Annu Rev Biochem*. 2015;84:577–601. doi: 10.1146/annurev-biochem-060614-034516.
16. Rybek MJ, Le J, Lodise TP, Levine DP, Brandley JS, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant staphylococcus aureus infections: a revised consensus guideline and review by the american society of health-system pharmacists, the infectious diseases society of america, the pediatric infectious diseases society, and the society of infectious diseases pharmacists. *Am J Health-Syst Pharm*. 2020;77(11):835-63. doi:10.1093/ajhp/zxaa036.
17. Martin-Loeches I, Guia MC, Vallecoccia MS, Suarez D, Ibarz M, et al. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. *Ann Intensive Care*. 2019;9(1):26. doi: 10.1186/s13613-019-0495-x.
18. Ibarz M, Haas LEM, Ceccato A, Artigas A. The critically ill older patient with sepsis: a narrative review. *Ann Intensive Care*. 2024;14(1):6. doi:10.1186/s13613-023-01233-7.
19. Wanrooij VHM, Cobussen M, Stoffers J, Buijs J, Bergmans DCJJ, et al. Sex differences in clinical presentation and mortality in emergency department patients with sepsis. *Ann Med*. 2023;55(2): 2244873. doi:10.1080/07853890.2023.2244873.

20. Lakbar I, Einav S, Lalevée N, Martin-Loeches I, Pastene B, et al. Interactions between Gender and Sepsis—Implications for the Future. *Microorganisms*. 2023;11(3):746. doi:10.3390/microorganisms11030746.

21. Maia MO, da Silveira CDG, Gomes M, Fernandes SES, Bezerra de Santana R, et al. Multidrug-Resistant Bacteria on Critically Ill Patients with Sepsis at Hospital Admission: Risk Factors and Effects on Hospital Mortality. *Infect Drug Resist*. 2023;16:1693-1704. doi: 10.2147/IDR.S401754.

22. Fadrian F, Linosefa L, Ridhwan FM, Hasnah H, Ayuni AS. Multidrug-Resistant Organisms and Determinant Factors in Sepsis Patients. *Iranian Journal of Medical Microbiology*. 2023;17(5):596-605. doi:10.30699/ijmm.17.5.596.

23. Jiang L, Cheng M. Impact of diabetes mellitus on outcomes of patients with sepsis: an updated systematic review and meta-analysis. *Diabetol Metab Syndr*. 2022;14(1):39. doi:10.1186/s13098-022-00803-2.

24. Hermiyanty. Faktor risiko infeksi saluran kemih di bagian rawat inap RSU Mokopido Tolitolitahun 2012. *Healthy Tadulako Journal*. 2016;2(2):53-59.

25. Howroyd F, Chacko C, MacDuff A, Gautam N, Pouchet B, et al. Ventilator-associated pneumonia: pathobiological heterogeneity and diagnostic challenges. *Nat Commun*. 2024;15(1):6447. doi: 10.1038/s41467-024-50805-z.

26. Gudiol C, Albasanz-Puig A, Cuervo G, Carratalà J. Understanding and Managing Sepsis in Patients With Cancer in the Era of Antimicrobial Resistance. *Front Med (Lausanne)*. 2021;8:636547. doi:10.3389/fmed.2021.636547.

27. Wang M, Jiang L, Zhu B, Li W, Du B, et al. The Prevalence, Risk Factors, and Outcomes of Sepsis in Critically Ill Patients in China: A Multicenter Prospective Cohort Study. *Front Med (Lausanne)*. 2020;7:593808. doi: 10.3389/fmed.2020.593808.

28. Ren Y, Zhang L, Xu F, Han D, Zheng S, et al. Risk factor analysis and nomogram for predicting in-hospital mortality in ICU patients with sepsis and lung infection. *BMC Pulm Med*. 2022;22:17. doi : 10.1186/s12890-021-01809-8.

29. Mustafai MM, Hafeez M, Munawar S, Basha S, Rabaan AA, et al. Prevalence of Carbapenemase and Extended-Spectrum β-Lactamase Producing *Enterobacteriaceae*: A Cross-Sectional Study. *Antibiotics (Basel)*. 2023;12(1):148. doi: 10.3390/antibiotics12010148.

30. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States*.; 2019.

31. Eichenberger EM, Thaden JT. Epidemiology and mechanisms of resistance of extensively drug resistant gram-negative bacteria. *Antibiotics*. 2019;8(2):37. doi:10.3390/antibiotics8020037.

32. Aurilio C, Sansone P, Barbarisi M, Pota V, Giaccari LG, et al. Mechanisms of Action of Carbapenem Resistance. *Antibiotics*. 2022;11(3):421. doi:10.3390/antibiotics11030421.

33. Eberhard A, Mellhammar L. Extended-spectrum beta-lactamase-producing Enterobacterales in patients with suspected sepsis in an acute care setting in Skåne, Sweden: a cohort study. *Infect Dis*. 2024;56(4):285-292. doi:10.1080/23744235.2023.2299676.

34. Kim HJ, Oh DK, Lim SY, Cho YJ, Park S, et al. Antibiogram of Multidrug-Resistant Bacteria Based on Sepsis Onset Location in Korea: A Multicenter Cohort Study. *J Korean Med Sci*. 2023;38(10):e75. doi: 10.3346/jkms.2023.38.e75.

35. Strich JR, Heil EL, Masur H. Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance. *The Journal of infectious diseases*. 2020;222(Suppl 2):S119–S131. doi: 10.1093/infdis/jiaa221.

36. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis*. 2017;64(6):e34-e65. doi: 10.1093/cid/ciw861.

37. Ospina-Tascón GA, Hernandez G, Alvarez I, Calderón-Tapia LE, Manzano-Nunez R, et al. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. *Crit Care*. 2020;24(1):52. doi: 10.1186/s13054-020-2756-3.

38. Xu J, Cai H, Zheng X. Timing of vasopressin initiation and mortality in patients with septic shock: analysis of the MIMIC-III and MIMIC-IV databases. *BMC Infect Dis.* 2023;23(1):199. doi: 10.1186/s12879-023-08147-6.

39. Lueangarun S, Leelarasamee A. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: a retrospective study. *Interdiscip Perspect Infect Dis*. 2012;12:56-62. doi: 10.1155/2012/765205.

40. Tic´ac M, Grubic Kezele T, Bubonja Šonje M. Impact of Appropriate Empirical Antibiotic Treatment on the Clinical Response of Septic Patients in Intensive Care Unit: A Single-Center Observational Study. *Antibiotics*. 2024;13:569. doi : 10.3390/antibiotics13060569.

41. Costantini E, Carlin M, Porta M, Brizzi MF. Type 2 diabetes mellitus and sepsis: state of the art, certainties and missing evidence. *Acta Diabetol*. 2021;58(9):1139-1151. doi:10.1007/s00592-021-01728-4.

42. Bonnet M, Lagier JC, Raoult D, Khelaifia S. Bacterial culture through selective and non-selective conditions: the evolution of culture media in clinical microbiology. *New Microbes New Infect*. 2020;34:100622. doi:10.1016/j.nmni.2019.100622.

43. Thakur R, Naga Rohith V, Arora JK. Mean SOFA Score in Comparison With APACHE II Score in Predicting Mortality in Surgical Patients With Sepsis. *Cureus*. 2023;15(3):e36653. doi: 10.7759/cureus.36653.

44. Gabbar MA, Amr Hassan. The Effect of Implementing the Sepsis Early Goal-Directed Therapy (EGDT) Protocol on Patient Mortality in the Hospital ICU in Cairo, Egypt. *Journal of Anesthesiology and Clinical Research*. 2024;5(2):585-589. doi:10.37275/jacr.v5i2.535.

45. Shapiro NI, Douglas IS, Brower RG, Brown SM, Exline MC, et al. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. *N Engl J Med*. 2023;388(6):499-510. doi: 10.1056/NEJMoa2212663.

46. Gharamti A, Samara O, Monzon A, Scherger S, DeSanto K, et al. Association between cytokine levels, sepsis severity and clinical outcomes in sepsis: a quantitative systematic review protocol. *BMJ Open*. 2021;11(8):e048476. doi: 10.1136/bmjopen-2020-048476.

47. Ilias I, Vassiliou AG, Keskinidou C, Vrettou CS, Orfanos S, et al. Changes in Cortisol Secretion and Corticosteroid Receptors in COVID-19 and Non COVID-19 Critically Ill Patients with Sepsis/Septic Shock and Scope for Treatment. *Biomedicines*. 2023;11(7):1801. doi: 10.3390/biomedicines11071801.

48. Siampa VN, Abadi S, Aman AM, Bakri S, Halim R, Zainuddin AA. Association between severity of sepsis and thyroid function profile. *Acta Biomedica*. 2023;94(6):e2023239. doi:10.23750/abm.v94i6.15076

49. Chang CM, Hsieh MS, Yang CJ, How CK, Chen PC, et al. Effects of empiric antibiotic treatment based on hospital cumulative antibiograms in patients with bacteraemic sepsis: a retrospective cohort study. *Clin Microbiol Infect*. 2023;29(6):765-771. doi: 10.1016/j.cmi.2023.01.004.

50. Martínez ML, Plata-Menchaca EP, Ruiz-Rodríguez JC, Ferrer R. An approach to antibiotic treatment in patients with sepsis. *J Thorac Dis*. 2020;12(3):1007-1021. doi:10.21037/jtd.2020.01.47.

51. Kim JY, Lee HY, Lee J, Oh DK, Lee SY, et al. Pre-Sepsis Length of Hospital Stay and Mortality: A Nationwide Multicenter Cohort Study. *J Korean Med Sci*. 2024;39(9):e87. doi: 10.3346/jkms.2024.39.e87.

52. Chen YJ, Chen FL, Chen JH, Wu MM, Chien DS, et al. Costs and length of sepsis-related hospitalizations in Taiwan. *Medicine*. 2020;99(22):e20476. doi: 10.1097/MD.0000000000020476.

53. Wahyuni, RD. Identifikasi bakteri udara pada instalasi radiologi rumah sakit umum daerah Undata Palu. *Healthy Tadulako Journal (Jurnal Kesehatan Tadulako)*. 2017;3(1):1-84.

54. Fadrian F, Ahmad A, Khairat K, Putri VY. The diagnostic value of the italian score for predicting extended-spectrum β lactamase- producing *enterobacterales* infection in sepsis patients at Dr. M. Djamil Central General Hospital Padang, Indonesia. *Biomedical and Biotechnology Research Journal*. 2024;8(Abstract Supplement):S28. doi: 10.4103/bbrj.bbrj_135_24.

55. Yungyuen T, Chatsuwan T, Plongla R, Kanthawong S, Yordpratum U, et al. Nationwide Surveillance and Molecular Characterization of Critically Drug-Resistant Gram-Negative Bacteria: Results of the Research University Network Thailand Study. *Antimicrob Agents Chemothe*r. 2021;65(9):e0067521. doi: 10.1128/AAC.00675-21.

56. Fadrian F, Aliska G, Utami WN. The relationship between appropriateness of antibiotic use based on the gyssens algorithm and mortality: a retrospective cohort study in Indonesian tertiary hospital. *Acta Med Indones*. 2024;56(2):137-144.