Journal of Medicinal and Chemical Sciences 7 (2024) 684-696

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Correlation between the Suitability of Empirical Antibiotic Therapy and Culture Results on Clinical Outcomes of Pneumonia Patients at Dr. Soetomo Regional Public Hospital, Surabaya

Suharyadi Sasmanto[1]*, Pepy Dwi Endraswari[2,3], SR Oktaviani Sulikah[2,3], Ni Made Mertaniasih[2,3], Tutik Kusmiati[3,4]

[1]*Study Program of Clinical Microbiology Specialist, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
[2]*Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
[3]*Dr. Soetomo Academic Hospital, Surabaya, Indonesia*
[4]*Department of Pulmonology and Respirology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*

ARTICLEINFO

Article history

Receive: 2023-12-21
Received in revised: 2024-01-22
Accepted: 2024-01-28
Manuscript ID: JMCS-2312-2407
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Majid Darroudi

DOI:10.26655/JMCHEMSCI.2024.5.2

KEYWORDS

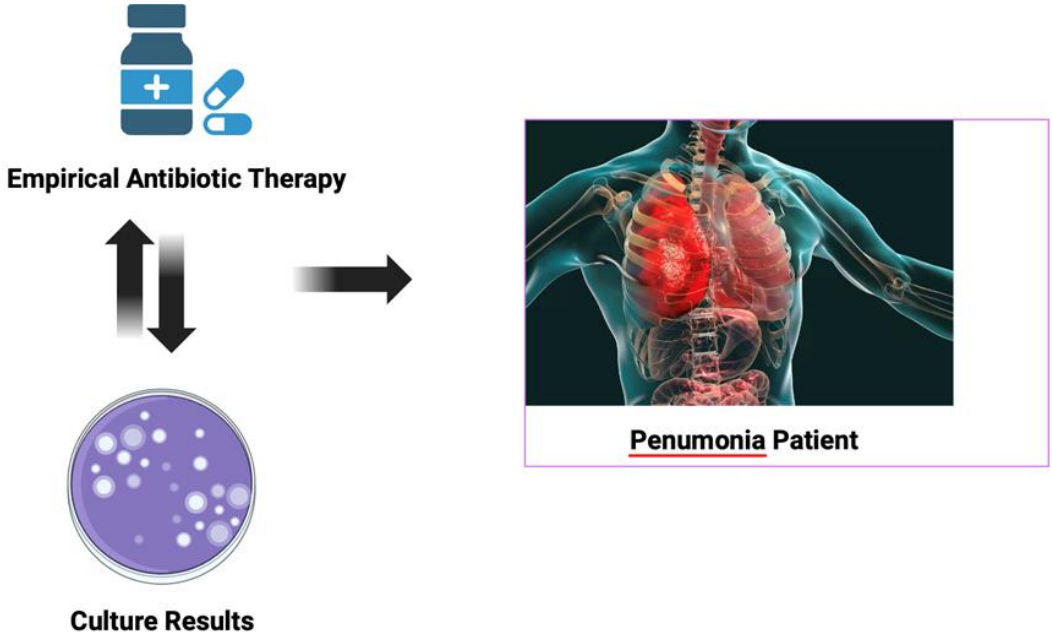
Pneumonia
Antibiotic
Bacteria
Sensitivity
Therapy

ABSTRACT

Pneumonia is a global health concern, causing significant morbidity and mortality, particularly among vulnerable populations. This study, conducted at Dr. Soetomo Regional Public Hospital (RSUD Dr. Soetomo), Surabaya, Indonesia, aimed to assess the causative pathogens, antibiotic sensitivity patterns, and the impact of empiric therapy on the clinical outcomes of pneumonia patients. The present study analyzed 324 cases from January to March 2023, categorizing pneumonia as community-acquired (CAP), hospital-acquired (HAP), and ventilator-associated (VAP). Gram-negative bacteria, predominantly *Klebsiella pneumoniae*, were the primary pathogens, with 44% being multidrug-resistant. Antibiotic sensitivity patterns highlighted the efficacy of *amikacin*, *cefoperazone sulbactam*, and *meropenem* against Gram-negative bacteria. Empiric therapy, mainly monotherapy, showed varied outcomes across pneumonia types. Clinical improvement was observed in 72.5% of CAP patients, while HAP and VAP patients faced challenges, with high mortality rates of 47.2% and 89.1%, respectively. Clinical stability in CAP correlated with age, culture results, multidrug resistance, pneumonia severity, and antibiotic class. In HAP, appropriate empiric therapy and pneumonia severity influenced clinical outcomes. Notably, VAP patients experienced poor outcomes irrespective of the variables studied. This study underscores the importance of local pathogen prevalence awareness and tailored empiric therapy to enhance pneumonia management, especially in HAP and VAP cases. Further research is warranted to refine treatment strategies and improve patient outcomes.

* Corresponding author: Suharyadi Sasmanto
✉ E-mail: ssasmanto1988@gmail.com

GRAPHICALABSTRACT



Introduction

Pneumonia is an infection of the lung parenchyma that significantly impacts global morbidity and mortality [1]. In 2019, approximately 2.5 million deaths were reported from pneumonia, with the 2019 Global Burden of Diseases (GBD) study noting that lower respiratory tract infections, including pneumonia and bronchiolitis, affected 489 million people worldwide, particularly children under five years of age and adults over 70 years [2]. In Indonesia, the Wolrd Health Organization (WHO) estimates 56,600 deaths per year due to lower respiratory tract infections, with pneumonia as the main cause of hospitalization and the highest crude fatality rate (CFR) at 7.6% [3]. The pneumonia proportion in hospital patients reached 19.9% in the Philippines, 6.4% in Malaysia, and 1.5% in Indonesia, with a higher risk of death from hospital-acquired pneumonia than community-acquired pneumonia in Southeast Asia [4].

Historical data categorizes pneumonia into community-acquired pneumonia (CAP) and nosocomial pneumonia, which is further differentiated into hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [5]. Recently, hospital-associated pneumonia includes patients who are not hospitalized but are regularly in contact with healthcare centers [6]. Pneumonia can be caused by various organisms, including bacteria, viruses, fungi, and parasites [7].

Infections in hospital environments involve pathogens that are more resistant to drugs than those involved in infections in community environments, and the cause of pneumonia is often challenging to identify, taking several days even with the invasive methods used in America, which only find the cause in 50% of cases [3]. Providing appropriate empiric therapy, including proper antibiotic selection, accurate timing, and dosing, plays a key role in effectively treating pneumonia [8].

Antibiotics administered within the first 4-8 hours of a patient's arrival at the hospital are associated with a 43% reduction in mortality, while therapy failure within the first 48-72 hours can increase the risk of death up to 11 times [9].

Despite advances in antimicrobial therapy, microbiological diagnostic tests, and preventive measures, pneumonia remains the leading cause of death from infectious diseases worldwide [10].

The emergence of multidrug-resistant (MDR) bacteria poses a serious challenge for clinicians and may lead to a "post-antibiotic era," where previously controlled infections can become a fatal threat [11]. Understanding the role of microorganisms that cause pneumonia, administering early antimicrobial therapy, and knowledge of the local prevalence of pathogens are crucial in selecting effective antimicrobials in the pneumonia treatment [12, 13].

Therefore, it is necessary to conduct research to determine the proportion of causative pathogens, patterns of antimicrobial sensitivity, and the relationship between the suitability of empiric antibiotic therapy and culture results on the clinical outcomes of pneumonia patients at Dr. Soetomo Regional Public Hospital (RSUD Dr. Soetomo), Surabaya.

Materials and Methods

Sampling

Samples were obtained from the microbiology data of the Clinical Microbiology Unit of Dr. Soetomo Regional Public Hospital, while medical record data was collected from the Medical Record Unit and the hospital's Management Information System. The study was conducted in July 2023 after obtaining ethical approval. This observational analytical study employed a retrospective cross-sectional design. The study population included patients diagnosed with pneumonia who submitted lower respiratory tract specimens to the Clinical Microbiology Laboratory of RSUD Dr. Soetomo. The sample consisted of pneumonia patients with lower respiratory tract specimens from January to March 2023, with 105 samples collected using a consecutive sampling technique from secondary data in the forms of medical records and clinical microbiology culture examination logbooks.

Inclusion criteria for this study included pneumonia patients who submitted specimens for aerobic culture examination with pathogen identification and antibiotic sensitivity testing, and also were over 18 years old. Meanwhile, exclusion criteria for this study included COVID-19 pneumonia patients without bacterial co-infection, aerobic culture results showing normal or fungal flora, and cases with a diagnosis of pneumonia that did not match the medical record.

Data collection procedures

The samples utilized in this study were chosen from the sputum sample examination logbook in the Sputum Division of the Clinical Microbiology Laboratory of RSUD Dr. Soetomo from January to March 2023. Sample selection was based on inclusion criteria, encompassing various aspects such as the classification of pneumonia, sepsis, germ pattern, empirical antibiotic sensitivity, degree of severity, and comorbidity factors. Information pertaining to clinical stability, length of stay, and mortality was also derived from the sample data. The entire dataset collected was subsequently analyzed in detail to assess the pattern of pathogens causing pneumonia, response to empiric antibiotics, and the impact of clinical factors on patient outcomes.

Data analysis

Data analysis in this study employed a descriptive approach to delineate patterns of causative pathogens, antibiotic sensitivities, patterns of empiric antibiotic administration, and the proportion of pneumonia events. The relationship between the suitability of empirical therapy with culture results and other variables was examined using the chi-square test, while differences in the length of stay were assessed using the independent t-test if the data were normally distributed.

Results and Discussion

Characteristics of pneumonia patients

This study encompassed 324 samples extracted from the medical records of patients diagnosed with pneumonia who submitted lower respiratory tract specimen cultures at RSUD Dr. Soetomo, Surabaya, during January-March 2023. Pneumonia diagnoses were categorized as community-acquired pneumonia (CAP) at 58.3%, hospital-acquired pneumonia (HAP) at 27.5%, and ventilator-associated pneumonia (VAP) at 14.2%. Most of the CAP patients exhibited non-severe pneumonia (76.2%), and more than half of

the HAP patients also fell into the non-severe pneumonia category (60.7%).

All of the VAP patients presented with severe degrees of pneumonia. Sepsis was identified at the onset of treatment in 32.1% of patients, and comorbidities were evident in 97.2% of patients, with diabetes mellitus, cerebral nerve and vascular disease, cardiovascular disease, and impaired renal function being the primary comorbidities. The majority of patients received treatment in low-care wards (64.5%). An overview of the characteristics of pneumonia patients is presented in Table 1.

Data analysis revealed that diabetes mellitus was the most prevalent comorbidity, identified in 33.9% of the 189 CAP patients. In addition, cardiovascular disease was present in 28% of patients and impaired renal function in 27% of patients. Among HAP patients, cerebral nerve and vascular disease were the most common comorbidities, detected in 43.8% of the 89 patients. Other comorbidities included cardiovascular disease (35.9%) and impaired renal function (35.8%). In VAP patients, cerebral nerve and vascular disease remained the most prevalent comorbidity, identified in 60.9% of the 46 VAP patients, followed by cardiovascular disease (26.1%) and diabetes mellitus (21.7%).

Table 1: Characteristics of pneumonia patients

Variables			Total (n = 324)	
			n	%
Age (year)	≤ 60		221	68.2%
	> 60		103	31.8%
	Median		55	
	Mean ± SD		52.52 + 15.92	
Sex	Male		202	62.3%
	Female		122	37.7%
Pneumonia	CAP		189	58.3%
	HAP		89	27.5%
	VAP		46	14.2%
Degree of Severity	CAP	Not Severe	144	76.2%
		Severe	45	23.8%
	HAP	Not Severe	54	60.7%
		Severe	35	39.3%
	VAP	Severe	46	100%
Diagnosis at the Beginning of Therapy			104	32.1%
With Comorbidities	Diabetes Mellitus		105	32.4%
	Brain Nerve and Blood Vessel Diseases		105	32.4%
	Cardiovascular Disease		97	29.9%
	Kidney Function Disorders		89	27.5%
	Malignancy		59	18.2%
	Tuberculosis		48	14.8%
	Pleural Effusion		39	12%
	Liver Function Disorders		28	8.6%
	Other Lung Diseases		14	4.3%
	COPD		9	2.8%
	Asthma		6	1.9%
With No Comorbidities			9	2.8%
Treatment Rooms	Low Care		209	64.5%
	High Care		115	35.5%

Table 2: Identification of bacteria causing CAP, HAP, and VAP

Identify the Causing Bacteria	Types of Pneumonia			
	CAP	HAP	VAP	n (%)
	n (%)	n (%)	n (%)	n (%)
Klebsiella pneumoniae	58 (30.7%)	26 (29.2%)	9 (19.6%)	93 (28.7%)
Pseudomonas aeruginosa	29 (15.3%)	18 (20.2%)	12 (26.1%)	59 (18.2%)
Acinetobacter baumannii	31 (16.4%)	13 (14.6%)	11 (23.9%)	55 (16.9%)
Eschericia coli	23 (12.2%)	9 (10.1%)	2 (4.3%)	34 (10.5%)
Enterobacter cloacae	12 (6.3%)	6 (6.7%)	3 (6.5%)	21 (6.5%)
Staphylococcus aureus	9 (4.8%)	8 (8.9%)	4 (8.7%)	21 (6.5%)
Stenotrophomonas Maltophilia	2 (1.05%)	1 (1.1%)	2 (4.3%)	5 (1.5%)
Klebsiella aerogenes	4 (2.2%)	-	-	4 (1.2%)
Klebsiella ozaenae	2 (1.05%)	2 (2.2%)	-	4 (1.2%)
Serratia marcessens	2 (1.05%)	2 (2.2%)	-	4 (1.2%)
Klebsiella oxytoca	2 (1.05%)	1 (1.1%)	-	3 (0.9%)
Aeromonas caviae	2 (1.05%)	-	-	2 (0.6%)
Aeromonas veronii	2 (1.05%)	-	-	2 (0.6%)
Citrobacter freundii	1 (0.5%)	1 (1.1%)	-	2 (0.6%)
Moraxella spp.	-	1 (1.1%)	1 (2.2%)	2 (0.6%)
Proteus mirabillis	2 (1.05%)	-	-	2 (0.6%)
Providencia stuartii	2 (1.05%)	-	-	2 (0.6%)
Pseudomonas putida	2 (1.05%)	-	-	2 (0.6%)
Citrobacter braaki	1 (0.5%)	-	-	1 (0.3%)
Corynebacterium matruchoti	1 (0.5%)	-	-	1 (0.3%)
Cronobacter sakazaki complex	1 (0.5%)	-	-	1 (0.3%)
Enterobacter aerogenes	1 (0.5%)	-	-	1 (0.3%)
Namhemia haemolitica	-	-	1 (2.2%)	1 (0.3%)
Neisseria animaloris	-	-	1 (2.2%)	1 (0.3%)
Salmonella enterica spp. arizonae	-	1 (0.3%)	-	1 (1.1%)
Total	189	89	46	324

Proportion of pathogens causing CAP, HAP, and VAP

The bacteria responsible for pneumonia in this study comprised both Gram-positive and Gram-negative bacteria, with a higher prevalence of Gram-negative bacteria. Gram-negative bacteria were identified in 93.2% (302 patients) of the total 324 pneumonia cases, while Gram-positive bacteria were present in 6.8% (22 patients). *Klebsiella pneumoniae* emerged as the most common Gram-negative bacteria, affecting 28.7% (93 patients), followed by *Pseudomonas aeruginosa* (18.2%), *Acinetobacter baumannii* (16.9%), *Escherichia coli* (10.5%), and *Enterobacter cloacae* (6.5%). *Staphylococcus aureus* played a significant role in Gram-positive pneumonia, accounting for 6.5% (21 patients).

Regarding pneumonia types, *Klebsiella pneumoniae* was the dominant pathogen in CAP (30.7%), HAP (29.2%), and VAP (26.1%) (Table 2). Forty-four percent of the bacterial pathogens identified in this study were multidrug-resistant (MDR), with 39.2% in CAP patients and 51.1% in nosocomial pneumonia (HAP and VAP).

Antibiotic sensitivity patterns of pathogens causing CAP, HAP, and VAP

Antibiotic sensitivity testing in pneumonia patients revealed the top five antibiotics exhibiting the highest sensitivity to Gram-negative bacteria: *amikacin* (87.6%), *cefoperazone sulbactam* (75.9%), *gentamicin*, *meropenem* (61.3% each), and *moxifloxacin* (55.9%). In contrast, Gram-negative bacteria displayed the highest resistance to *ampicillin* (99.3%), *cefazolin* (85.5%), *amoxicillin-clavulanate* (74.3%), *ciprofloxacin* (73.9%), and *chloramphenicol* (72.2%).

Table 3: Antibiotic sensitivity patterns according to the most common bacteria

Bacterial Identification	Antibiotic Sensitivity Test Pattern	
	Sensitive n (%)	Resistant n (%)
Enterobactericeae spp. (n = 171)	*Amikacin* 164/169 (97%)	*Ciprofloxacin* 87/88 (98.9%)
	Cefoperazone sulbactam 140/166 (84.3%)	*Ampicillin* 166/168 (98.8%)
	Gentamicin 124/168 (73.8%)	*Levofloxacin* 65/67 (97%)
	Fosfomycin 119/162 (73.5%)	*Cefazolin* 123/165 (74.5%)
	Meropenem 99/163 (60.7%)	*Piperacillin* 118/169 (69.8%)
Pseudomonas spp. (n = 61)	*Amikacin* 56/61 (91.8%)	*Amoxicillin clavulanate* 61/61 (100%)
	Cefoperazone sulbactam 47/57 (82.5%)	*Ampicillin* 61/61 (100%)
	Meropenem 45/59 (76.3%)	*Chloramphenicol* 61/61 (100%)
	Piperacillin tazobactam 39/60 (65%)	*Cefotaxime* 61/61 (100%)
	Imipenem 38/59 (64.4%)	*Ampicillin sulbactam* 61/61 (100%)
Acinetobacter spp. (n = 55)	*Amikacin* 34/55 (61.8%)	*Amoxicillin clavulanate* 55/55 (100%)
	Cotrimoxazole 32/52 (61.5%)	*Aztreonam* 55/55 (100%)
	Meropenem 28/52 (53.8%)	*Ceftriaxone 55/55 (100%)*
	Imipenem 25/50 (50%)	*Ampicillin 55/55 (100%)*
	Cefoperazone sulbactam 26/55 (47.3%)	*Chloramphenicol* 55/55 (100%)
Staphylococcus spp. (n = 21)	*Mupirocin high level* 20/21 (95.2%)	*Ampicillin* 18/19 (94.7%)
	Cotrimoxazole 19/21 (90.5%)	*Penicillin* 17/20 (85%)
	Vancomycin 17/20 (85%)	*Chloramphenicol* 10/18 (55.5%)
	Ciprofloxacin 17/20 (85%)	*Cefoxitin* 9/17 (52.9%)
	Linezolid 14/21 (66.7%)	*Clindamycin* 11/21 (52.4%)

Table 4: Outcomes by type of pneumonia

Types of Pneumonia	Clinical Stability		Length of Stay		Mortality	
	Improvement	Worsening	Median	Mean ± SD	Recover	Die
CAP	137 (72.5%)	52 (27.5%)	9	9.85 ± 6.6	144 (76.2%)	45 (23.8%)
HAP	43 (48.3%)	46 (51.7%)	9	11.34 ± 9.2	47 (52.8%)	42 (47.2%)
VAP	4 (8.7%)	42 (91.3%)	8.5	10.2 ± 7.9	5 (10.9%)	41 (89.1%)

Among Gram-positive bacteria, *mupirocin high level* (95.2%), *cotrimoxazole* (86.4%), *vancomycin* (85.7%), *ciprofloxacin* (85%), and *fosfomycin* (77.8%) exhibited high sensitivity. The highest resistance in Gram-positive bacteria occurred with *ampicillin* (94.7%), *penicillin* (85.7%), *tetracycline* (66.7%), *clindamycin* (54.5%), and *cefoxitin* (52.9%).

Analysis of antibiotic sensitivity patterns based on bacterial families revealed variations in responses to *Enterobacteriaceae spp.*, *Pseudomonas spp.*, *Acinetobacter spp.*, and *Staphylococcus spp*. Antibiotics displaying high sensitivity for each bacterial family are summarized in Table 3.

In CAP patients with suspected Gram-negative bacteria, the antibiotics with the highest sensitivity were *amikacin* (92.2%) and *cefoperazone sulbactam* (83.8%), while for Gram-positive bacteria, the highest sensitivity was observed with *vancomycin* (77.8%) and *linezolid* (70%). Among HAP patients, antibiotics with high sensitivity for Gram-negative bacteria included *amikacin* (87.3%) and *cefoperazone sulbactam* (70%), whereas for Gram-positive bacteria, *vancomycin* (100%) and *linezolid* (75%) exhibited high sensitivity. The highest resistance in HAP patients was recorded for *ampicillin* (98.8%), *cefazolin* (88.3%), and *penicillin* (87.5%).

In VAP patients, *amikacin* (68.3%) and *cefoperazone sulbactam* (52.6%) demonstrated high sensitivity to Gram-negative bacteria, while *vancomycin* (75%) exhibited sensitivity to Gram-positive bacteria. The highest resistance in VAP patients was noted for *ampicillin* (100%), *cefazolin* (89.7%), and *penicillin* (100%).

Empirical antibiotic therapy administration patterns in CAP, HAP, and VAP patients

In this study, pneumonia patients underwent empiric therapy, including monotherapy and combination therapy. Among the 45 patients with severe CAP, 75.6% received monotherapy, predominantly with beta-lactams (38.2%) and fluoroquinolones (32.3%). Combination therapy was administered to 24.4% of patients, involving combinations of beta-lactams with fluoroquinolones and beta-lactams with nitroimidazole. In the case of 138 patients with non-severe CAP, 95.8% received monotherapy, primarily with beta-lactams (36.2%) and fluoroquinolones (15.2%), while only 4.2% received combination therapy. Among patients with severe HAP, 77.1% received monotherapy, with beta-lactam (22.2%) and fluoroquinolone (40.7%) being the predominant choices. Combination therapy was administered to 22.9% of patients. In the subset of 54 non-severe HAP patients, 92.6% received monotherapy, mainly with beta-lactams (34%) and fluoroquinolones (20%), with only 7.4% opting for combination therapy.

In the case of 46 patients with severe VAP, 91.3% received monotherapy, with fluoroquinolones (35.7%), beta-lactams (26.2%), and glycopeptides (2.4%) being the main choices. Combination therapy was employed in 8.7% of patients, with the most common combination involving fluoroquinolones and beta-lactams.

Distribution and correlation of correspondence of empirical antibiotic therapy with culture results on clinical outcomes of CAP, HAP, and VAP patients

In this study, out of a total of 189 CAP patients, 72.5% experienced clinical improvement, while 27.5% experienced worsening. The average length of stay for CAP patients was 9.85 ± 6.6 days, with a cure rate of 76.2% and a death rate of 23.8%. Conversely, more HAP patients experienced worsening (51.7%) than improvement (48.3%), with a mean length of stay of 11.34 ± 9.2 days, a cure rate of 52.8%, and a death rate of 47.2%. In VAP patients, the majority experienced clinical worsening (91.3%), with a mean length of stay of 10.2 ± 7.9 days. The recovery rate was only 10.9%, while the death rate reached 89.1%. The comprehensive data on clinical outcomes by type of pneumonia are listed in Table 4.

This study explores the relationship between clinical outcomes in pneumonia patients and various potential variables. Clinical outcomes were primarily focused on clinical stability, length of stay, and mortality, while considered variables included age, number of comorbidities, Gram staining results of the culture, MDR pathogens, appropriateness of empiric therapy, degree of pneumonia, and class of empirical antibiotic therapy. In CAP patients, clinical stability and mortality exhibited significant associations with age ($p = 0.001$), culture Gram stain ($p = 0.001$), MDR pathogen ($p = 0.016$), pneumonia grade ($p = 0.000$), and empiric therapy group ($p = 0.016$). However, the appropriateness of empirical therapy did not demonstrate a significant relationship with clinical outcomes ($p > 0.05$).

For HAP patients, clinical stability was related to the appropriateness of empiric therapy ($p = 0.015$) and the degree of pneumonia ($p = 0.000$), while mortality was only associated with the degree of pneumonia ($p = 0.000$). Length of stay did not show a significant relationship with any variables. Age, number of comorbidities, Gram staining results of the culture, MDR pathogens, and class of empirical antibiotic therapy did not correlate with clinical outcomes in HAP patients ($p > 0.05$). In VAP patients, clinical stability, mortality, and length of stay did not show a significant relationship with variables such as age, number of comorbidities, Gram culture staining, MDR pathogens, appropriateness of empirical therapy, degree of pneumonia, and class of empirical antibiotic therapy ($p > 0.05$).

Early empiric therapy plays a crucial role in treating pneumonia, yet selecting the appropriate therapy remains challenging due to the diverse range of pathogens causing infections. Dynamic microbial patterns, population changes, comorbidities, and antibiotic usage patterns can all impact the success of therapy [14-16]. Research data indicate that the average age of pneumonia patients is approximately 52 years, with a higher proportion being men. Unlike the United States, Europe's highest incidence of pneumonia occurs at ages 65-79 years and over 80 years [17]. This difference may be influenced by variations in vaccination coverage and lifestyle factors such as smoking [18]. Notably, pneumococcal vaccination is not yet mandatory in Indonesia [19]. High comorbidities, such as cardiovascular disease, diabetes mellitus, cancer, and chronic obstructive pulmonary disease, significantly impact pneumonia cases in Indonesia [20]. The higher risk of pneumonia development in men compared to women may be attributed to differences in anatomical organs, behavior, socioeconomic status, and lifestyle factors [21].

Data from this study also revealed a predominance of non-severe grades in CAP and HAP patients at the time of diagnosis. In Europe, approximately 1.2%-10% of pneumonia patients requiring hospitalization progress to severe pneumonia, necessitating intensive care unit (ICU) admission [22]. Among individuals over 70 years of age with severe pneumonia, the 28-day mortality rate is reported to be 17% [23]. Comorbidities such as diabetes, hypertension, and cardiovascular disease can increase the risk and influence the clinical outcomes of pneumonia [24-26].

Understanding local pathogen prevalence is crucial for targeted antibiotic therapy. In this study, Gram-negative bacteria, particularly *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*, were predominant as causes of pneumonia. Global data indicates that *S. pneumoniae*, *P. aeruginosa*, and *K. pneumoniae* are the most common bacteria causing Community-Acquired Pneumonia (CAP) [27, 28]. Recognizing these patterns is essential to mitigate antibiotic resistance and reduce healthcare costs [28].

For Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP), aerobic Gram-negative bacilli (such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp.*, and *Acinetobacter spp.*) and Gram-positive cocci (such as *Staphylococcus aureus*, including Methicillin-Resistant *Staphylococcus aureus* (MRSA), and *Streptococcus spp.*) are the main pathogens [29]. The causative pathogen pattern is influenced by factors such as patient condition and local hospital flora [30].

In cases of pneumonia with comorbid diabetes mellitus, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* are prevalent. Research by [31] indicates that *K. pneumoniae* is the most common causative pathogen in pneumonia patients with diabetes. In contrast [32] demonstrated different pathogens in CAP and HAP patients with diabetes.

Pneumonia patients with cerebral nerve and vascular disease often exhibit dominance of *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *Staphylococcus aureus* [33]. Adjusting empiric antibiotic administration based on Gram stain examination results of lower respiratory specimens can aid in narrowing down antibiotic choices before culture results are known, facilitating more targeted treatment [34].

Sensitivity tests indicate the efficacy of several antibiotics against Gram-negative bacteria (such as *amikacin*, *cefoperazone sulbactam*, *gentamicin*, *meropenem*, and *moxifloxacin*) and Gram-positive bacteria (*mupirocin high level*, *cotrimoxazole*, *vancomycin*, *ciprofloxacin*, and *fosfomycin*). Multidrug-resistant (MDR) pathogens are identified in 44% of all pneumonia patients, with the primary risks in Community-Acquired Pneumonia (CAP) patients involving immunosuppression, previous antibiotic use, and a history of hospitalization [35].

Antibiotic resistance poses a significant challenge in HAP and VAP. Risk factors include local epidemiological conditions, patient-specific risk factors, and the presence of previous MDR pathogen colonization or infection [28]. Bacteria commonly found in pneumonia patients in this study include *Enterobacteriaceae spp.*, *Pseudomonas spp.*, *Acinetobacter spp.*, and

Staphylococcus spp., with documented sensitivity to specific antibiotics.

In this study, empiric therapy for pneumonia primarily consisted of monotherapy, although ATS/IDSA guidelines recommend combination therapy in hospitalized patients with severe CAP. A standard regimen of beta-lactam plus a *macrolide* or *fluoroquinolone* is commonly chosen, with the addition of *vancomycin* or *linezolid* if there is the MRSA history, and anti-pseudomonas agents if there is a history of *P. aeruginosa*. For HAP patients at high risk of death, the recommended therapy involves a combination of *piperacillin-tazobactam*, *cefepime/ceftazidime*, *levofloxacin/ciprofloxacin*, *imipenem/meropenem*, *amikacin/gentamicin/tobramycin*, *aztreonam* plus *vancomycin* or *linezolid* [29].

Empiric therapy may take the form of monotherapy or a combination of antibiotics. While combination therapy aims to broaden pathogen coverage and enhance effectiveness, it carries the risk of side effects and resistance. Studies vary in their findings, but overall, combination therapy does not consistently offer superior benefits [36] found in their research on CAP patients with *S. pneumoniae* infection that there was no significant difference in mortality between monotherapy and combination therapy. However, patients receiving combination therapy did experience a significant increase in length of stay.

The impact of empiric therapy on pneumonia outcomes varies across studies, making it challenging to draw definitive conclusions. Monotherapy is recommended for mild or moderate pneumonia cases without risk factors. In cases of moderate-severe pneumonia with bacteremia, risk factors, or atypical bacterial involvement, empiric monotherapy may prove inadequate. Research by De [37] in moderate-severe CAP patients found no significant difference in 30-day mortality between empiric therapy with moxifloxacin monotherapy and moxifloxacin combination therapy.

In this study, CAP patients generally exhibited clinical improvement within 72 hours after receiving empiric therapy, with an average length of stay of 9.85 days and a high cure rate. In contrast, HAP patients tended to experience clinical deterioration with an average length of stay of 11.34 days, possibly due to late diagnosis. VAP patients, on the other hand, almost universally experienced clinical deterioration, likely attributed to severe comorbid factors. This aligns with research by [38] in *P. aeruginosa* VAP patients in the ICU, where patients on combination therapy required mechanical ventilation for an average of 28 ± 12 days, as opposed to 23 ± 11 days in patients receiving monotherapy. The results indicated that clinical stability in CAP was associated with age, Gram staining results of the culture, MDR pathogens, degree of pneumonia, and class of empirical antibiotic therapy. Mortality/recovery rates were related to the same factors, and length of stay was only significantly related to the number of comorbidities. This aligns with research [39] at Fatmawati Central Public Hospital (RSUP Fatmawati), Jakarta, where patients receiving empiric antibiotics according to culture experienced more improvement, although no significant relationship was found between the use of empiric antibiotics and the clinical outcomes of CAP patients. In the context of HAP patients in this study, clinical stability was found to be associated with the appropriateness of empiric therapy ($p = 0.015$) and the degree of pneumonia ($p = 0.000$). Similarly, the mortality/cure rate exhibited a correlation with the degree of pneumonia ($p = 0.000$), while the average length of stay did not demonstrate a significant relationship with other variables. This aligns with the findings of Apriliany *et al.* [40], which identified a significant relationship between the appropriateness of empirical antibiotic use and the clinical outcomes of HAP patients. Moreover, the average length of stay for HAP patients was significantly correlated with the accuracy of empirical antibiotics administered. Contrasting results were found in Nasution and Wisudarti's [41] research on HAP patients in the ICU. They observed that patients receiving appropriate empiric antibiotics had high mortality, although this was not statistically significant. The length of stay of HAP patients in the ICU also did not exhibit a significant relationship with the appropriateness of empiric

antibiotics. Several factors, such as comorbid conditions, complications, and therapy not in accordance with guidelines, can influence the time required to achieve clinical stability in pneumonia. Menéndez *et al.*'s research [42] indicated that predictor factors for clinical stability encompass various aspects, including pleural effusion, multilobe infiltrate, pneumonia severity, chronic bronchitis, cardiac complications, empyema, ICU care, and therapeutic concordance.

While acknowledging the retrospective nature of this study with the potential for data gaps, its strength lies in the sample size, encompassing the proportion of pneumonia patients at RSUD Dr. Soetomo, Surabaya. The results offer insights into germ patterns, antibiotic sensitivity, patterns of empirical therapy administration, and pneumonia outcomes. For future studies, a prospective approach with a larger sample size and more selective inclusion criteria could provide further insights.

Conclusion

This study provides valuable insights into the characteristics of pneumonia patients at RSUD Dr. Soetomo Surabaya. The majority of patients were approximately 52.52 years old, predominantly male, and frequently presented with comorbidities such as diabetes mellitus and cerebral nerve and blood vessel diseases. CAP accounted for 58.3%, HAP for 27.5%, and VAP for 14.2%. *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* emerged as the primary bacteria in each pneumonia type. Gram-negative bacteria, notably *Klebsiella pneumoniae*, exhibited sensitivity to antibiotics such as *amikacin* and *cefoperazone sulbactam*, while Gram-positive bacteria responded effectively to *vancomycin* and *linezolid*. Empiric therapy predominantly took the form of monotherapy, particularly in severe VAP cases. Evaluation of patient outcomes demonstrated that antibiotic therapy tailored to culture results contributed to clinical improvement, although discordant results did not significantly impact outcomes.

The relationship between clinical stability, mortality, and length of stay varied across pneumonia types, with several influencing variables including age, degree of pneumonia, and appropriateness of empiric therapy. Despite study limitations, the results offer valuable insights into germ patterns, antibiotic sensitivity, and the influence of specific factors on the prognosis of pneumonia patients in the context of RSUD Dr. Soetomo Surabaya.

Acknowledgements

The authors would like to thank Jalan Tengah, Indonesia (http://jalantengah.site/) for editing the article.

ORCID

Suharyadi Sasmanto
https://www.orcid.org/0000-0002-8597-4212
Pepy Dwi Endraswari
https://www.orcid.org/0000-0002-0271-8505
SR Oktaviani Sulikah
https://www.orcid.org/0000-0002-6872-4908
Ni Made Mertaniasih
https://www.orcid.org/0000-0002-0594-2385
Tutik Kusmiati
https://www.orcid.org/0000-0001-8489-7000

References

[1]. Poovieng J., Sakboonyarat B., Nasomsong W., Bacterial etiology and mortality rate in community-acquired pneumonia, healthcare-associated pneumonia and hospital-acquired pneumonia in Thai university hospital, *Scientific Reports*, 2022, **12**:9004 [Crossref], [Google Scholar], [Publisher]

[2]. Vos T., Lim S.S., Abbafati C., Abbas K.M., Abbasi M., Abbasifard M., Abbasi-Kangevari M., Abbastabar H., Abd-Allah F., Abdelalim A., Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, *The lancet*, 2020, **396**:1204 [Crossref], [Google Scholar], [Publisher]

[3]. Indonesia P.D.P., Pedoman diagnosis dan penatalaksanaan di Indonesia, *Jakarta: Indah Offset Citra Grafika*, 2006, 1 [Google Scholar]

[4]. Isbaniah F., Handayani D. Hospital acquired pneumonia (HAP) dan ventilator associated pneumonia (VAP) pedoman diagnosis dan penatalaksanaan di Indonesia. 2018 [Google Scholar], [Publisher]
[5]. Jeon E.J., Cho S.G., Shin J.W., Kim J.Y., Park I.W., Choi B.W., Choi J.C., The difference in clinical presentations between healthcare-associated and community-acquired pneumonia in university-affiliated hospital in Korea, *Yonsei medical journal*, 2011, **52**:282 [Crossref], [Google Scholar], [Publisher]
[6]. Szabó S., Feier B., Capatina D., Tertis M., Cristea C., Popa A., An overview of healthcare associated infections and their detection methods caused by pathogen bacteria in Romania and Europe, *Journal of Clinical Medicine*, 2022, **11**:3204 [Crossref], [Google Scholar], [Publisher]
[7]. Lim W.S. Pneumonia-Overview. *Elsevier*, 2022, 185 [Crossref], [Google Scholar], [Publisher]
[8]. Wilson K.C., Schünemann H.J., An appraisal of the evidence underlying performance measures for community-acquired pneumonia, *American journal of respiratory and critical care medicine*, 2011, **183**:1454 [Crossref], [Google Scholar], [Publisher]
[9]. Beatty J.A., Majumdar S.R., Tyrrell G.J., Marrie T.J., Eurich D.T., Prognostic factors associated with mortality and major in-hospital complications in patients with bacteremic pneumococcal pneumonia: Population-based study, *Medicine*, 2016, **95**:e5179 [Crossref], [Google Scholar], [Publisher]
[10]. Cilloniz C., Ceccato A., San Jose A., Torres A., Clinical management of community acquired pneumonia in the elderly patient, *Expert Review of Respiratory Medicine*, 2016, **10**:1211 [Crossref], [Google Scholar], [Publisher]
[11]. Terreni M., Taccani M., Pregnolato M., New antibiotics for multidrug-resistant bacterial strains: latest research developments and future perspectives, *Molecules*, 2021, **26**:2671 [Crossref], [Google Scholar], [Publisher]
[12]. Mantero M., Tarsia P., Gramegna A., Henchi S., Vanoni N., Di Pasquale M., Antibiotic therapy, supportive treatment and management of immunomodulation-inflammation response in community acquired pneumonia: review of recommendations, *Multidisciplinary Respiratory Medicine*, 2017, **12**:1 [Crossref], [Google Scholar], [Publisher]
[13]. Grief S.N., Loza J.K., Guidelines for the Evaluation and Treatment of Pneumonia, *Primary Care: Clinics in Office Practice*, 2018, **45**:485 [Crossref], [Google Scholar], [Publisher]
[14]. Shindo Y., Ito, R., Kobayashi, D., Ando, M., Ichikawa, M., Goto, Y., Fukui, Y., Iwaki, M., Okumura, J.,Yamaguchi, I., Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: an observational cohort study, *The Lancet infectious diseases*, 2015, **15**:1055 [Crossref], [Google Scholar], [Publisher]
[15]. Dillon K., Garnick B., Fortier M., Felicia B., Fulton A., Dumont C., Dorval B., Gardella K., The Management of Infectious Pulmonary Processes in the Emergency Department: Pneumonia, *Physician Assistant Clinics*, 2023, **8**:123 [Crossref], [Google Scholar], [Publisher]
[16]. Vaithiyam V.S., Rastogi N., Ranjan P., Mahishi N., Kapil A., Dwivedi S.N., Soneja M., Wig N., Biswas A., Antimicrobial resistance patterns in clinically significant isolates from medical wards of a tertiary care hospital in North India, *Journal of laboratory physicians*, 2020, **12**:196 [Crossref], [Google Scholar], [Publisher]
[17]. Torres A., Peetermans W.E., Viegi G., Blasi F., Risk factors for community-acquired pneumonia in adults in Europe: a literature review, *Thorax*, 2013, **68**:1057 [Crossref], [Google Scholar], [Publisher]
[18]. Jamal A., Phillips E., Gentzke A.S., Homa D.M., Babb S.D., King B.A., Neff L.J., Current cigarette smoking among adults—United States, 2016, *Morbidity and Mortality Weekly Report*, 2018, **67**:53 [Crossref], [Google Scholar], [Publisher]
[19]. Kartasasmita C.B., Rezeki Hadinegoro S., Kurniati N., Triasih R., Halim C., Gamil A., Epidemiology, nasopharyngeal carriage, serotype prevalence, and antibiotic resistance of Streptococcus pneumoniae in Indonesia, *Infectious Diseases and Therapy*, 2020, **9**:723 [Crossref], [Google Scholar], [Publisher]
[20]. Wahidin M., Agustiya R.I., Putro G., Beban penyakit dan program pencegahan dan pengendalian penyakit tidak menular di

indonesia, *J Epidemiol Kesehat Indones*, 2023, **6** [Google Scholar], [Publisher]
[21]. Corica B., Tartaglia F., D'Amico T., Romiti G.F., Cangemi R., Sex and gender differences in community-acquired pneumonia, *Internal and Emergency Medicine*, 2022, **17**:1575 [Crossref], [Google Scholar], [Publisher]
[22]. Walden A.P., Clarke G.M., McKechnie S., Hutton P., Gordon A.C., Rello J., Chiche J.D., Stueber F., Garrard C.S., Hinds C.J., Patients with community acquired pneumonia admitted to European intensive care units: an epidemiological survey of the GenOSept cohort, *Critical care*, 2014, **18**:1 [Crossref], [Google Scholar], [Publisher]
[23]. Morgan A., Glossop A., Severe community-acquired pneumonia, *Bja Education*, 2016, **16**:167 [Crossref], [Google Scholar], [Publisher]
[24]. Ghia C.J., Rambhad G.S., Systematic review and meta-analysis of comorbidities and associated risk factors in Indian patients of community-acquired pneumonia, *SAGE Open Medicine*, 2022, **10**:20503121221095485 [Crossref], [Google Scholar], [Publisher]
[25]. Kassaw G., Mohammed R., Tessema G.M., Yesuf T., Lakew A.M., Tarekegn G.E., Outcomes and Predictors of Severe Community-acquired Pneumonia Among Adults Admitted to the University of Gondar Comprehensive Specialized Hospital: A Prospective Follow-up Study, *Infection and drug resistance*, 2023, 619 [Crossref], [Google Scholar], [Publisher]
[26]. Yakoub M., Elkhwsky F., El Tayar A., El Sayed I., Hospital-acquired pneumonia pattern in the intensive care units of a governmental hospital: A prospective longitudinal study, *Annals of African medicine*, 2023, **22**:94 [Crossref], [Google Scholar], [Publisher]
[27]. Carugati M., Aliberti S., Sotgiu G., Blasi F., Gori A., Menendez R., Encheva M., Gallego M., Leuschner P., Ruiz-Buitrago S., Bacterial etiology of community-acquired pneumonia in immunocompetent hospitalized patients and appropriateness of empirical treatment recommendations: an international point-prevalence study, *European Journal of Clinical Microbiology & Infectious Diseases*, 2020, **39**:1513 [Crossref], [Google Scholar], [Publisher]
[28]. Torres A., Cilloniz C., Niederman M.S., Menendez R., Chalmers J.D., Wunderink R.G., van der Poll T., Pneumonia, *Nature Reviews Disease Primers*, 2021, **7**:1 [Crossref], [Google Scholar], [Publisher]
[29]. Kalil A.C., Metersky M.L., Klompas M., Muscedere J., Sweeney D.A., Palmer L.B., Napolitano L.M., O'Grady N.P., Bartlett J.G., Carratalà J., Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society, *Clinical Infectious Diseases*, 2016, **63**:e61 [Crossref], [Google Scholar], [Publisher]
[30]. Feng D.Y., Zhou Y.Q., Zou X.L., Zhou M., Zhu J.X., Wang Y.H., Zhang T.T., Differences in microbial etiology between hospital-acquired pneumonia and ventilator-associated pneumonia: a single-center retrospective study in Guang Zhou, *Infection and drug resistance*, 2019, 993 [Crossref], [Google Scholar], [Publisher]
[31]. Saibal M., Rahman S., Nishat L., Sikder N., Begum S., Islam M., Uddin K., Community acquired pneumonia in diabetic and non-diabetic hospitalized patients: presentation, causative pathogens and outcome, *Bangladesh Medical Research Council Bulletin*, 2012, **38**:98 [Crossref], [Google Scholar], [Publisher]
[32]. López-de-Andrés A., Perez-Farinos N., de Miguel-Díez J., Hernández-Barrera V., Jiménez-Trujillo I., Méndez-Bailón M., de Miguel-Yanes J.M., Jiménez-García R., Type 2 diabetes and postoperative pneumonia: an observational, population-based study using the Spanish Hospital Discharge Database, 2001-2015, *PloS one*, 2019, **14**:e0211230 [Crossref], [Google Scholar], [Publisher]
[33]. Lee H.S., Moon J., Shin H.R., Ahn S.J., Kim T.J., Jun J.S., Lee S.T., Jung K.H., Park K.I., Jung K.Y., Pneumonia in hospitalized neurologic patients: trends in pathogen distribution and antibiotic susceptibility, *Antimicrobial Resistance & Infection Control*, 2019, **8**:1 [Crossref], [Google Scholar], [Publisher]
[34]. Gunasekaran J., Saksena R., Jain M., Gaind R., Can sputum gram stain be used to predict lower respiratory tract infection and guide empiric antimicrobial treatment: Experience from a

tertiary care hospital, *Journal of microbiological methods*, 2019, **166**:105731 [Crossref], [Google Scholar], [Publisher]
[35]. Shindo Y., Ito R., Kobayashi D., Ando M., Ichikawa M., Shiraki A., Goto Y., Fukui Y., Iwaki M., Okumura J., Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia, *American journal of respiratory and critical care medicine*, 2013, **188**:985 [Crossref], [Google Scholar], [Publisher]
[36]. Chokshi R., Restrepo M., Weeratunge N., Frei C., Anzueto A., Mortensen E., Monotherapy versus combination antibiotic therapy for patients with bacteremic Streptococcus pneumoniae community-acquired pneumonia, *European Journal of Clinical Microbiology & Infectious Diseases*, 2007, **26**:447 [Crossref], [Google Scholar], [Publisher]
[37]. De la Calle C., Ternavasio-de la Vega H., Morata L., Marco F., Cardozo C., García-Vidal C., Del Rio A., Cillóniz C., Torres A., Martínez J.A., Effectiveness of combination therapy versus monotherapy with a third-generation cephalosporin in bacteraemic pneumococcal pneumonia: a propensity score analysis, *Journal of Infection*, 2018, **76**:342 [Crossref], [Google Scholar], [Publisher]
[38]. Foucrier A., Dessalle T., Tuffet S., Federici L., Dahyot-Fizelier C., Barbier F., Pottecher J., Monsel A., Hissem T., Lefrant J.Y., Association between combination antibiotic therapy as opposed as monotherapy and outcomes of ICU patients with Pseudomonas aeruginosa ventilator-associated pneumonia: an ancillary study of the iDIAPASON trial, *Critical care*, 2023, **27**:211 [Crossref], [Google Scholar], [Publisher]
[39]. Setiadi F., Oktovina M.N., Salamah U., Fadillah T.N. Hubungan penggunaan antibiotik empiris terhadap outcome terapi pasien community acquired pneumonia (CAP) di RSUP Fatmawati Jakarta the relationship of empirical antibiotic use to the therapeutic outcomes of community acquired pneumonia (CAP) patients. 2021, **3**:261 [Crossref], [Google Scholar], [Publisher]
[40]. Apriliany F., Umboro R.O., Ersalena V.F., Rasionalitas antibiotik empiris pada pasien hospital acquired pneumonia (HAP) di RSUD provinsi NTB, *Majalah Farmasi dan Farmakologi*, 2022, **26**:26 [Crossref], [Google Scholar], [Publisher]
[41]. Nasution R.A., Wisudarti C.F.R., Hubungan Antara Kesesuaian Terapi Antibiotik Empiris Dengan Mortalitas Rumah Sakit Pada Pasien Hospital Acquired Pneumonia Yang Dirawat DI ICU RSUP DR SARDJITO YOGYAKARTA, *Jurnal Komplikasi Anestesi*, **5**:21 [Crossref], [Google Scholar], [Publisher]
[42]. Menéndez R., Cavalcanti M., Reyes S., Mensa J., Martinez R., Marcos M.A., Filella X., Niederman M., Torres A., Markers of treatment failure in hospitalized community-acquired Pneumonia, *Thorax*, 2008, **5**:447 [Crossref], [Google Scholar], [Publisher]

HOW TO CITE THIS ARTICLE
Suharyadi Sasmanto*, Pepy Dwi Endraswari, SR Oktaviani Sulikah, Ni Made Mertaniasih, Tutik Kusmiati, Correlation between the Suitability of Empirical Antibiotic Therapy and Culture Results on Clinical Outcomes of Pneumonia Patients at Dr. Soetomo Regional Public Hospital, Surabaya. *J. Med. Chem. Sci.*, 2024, 7(5) 684-696.
DOI: https://doi.org/10.26655/JMCHEMSCI.2024.5.2
URL: https://www.jmchemsci.com/article_189961.html