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Sensitivity of Bacteria causing Hospital-Acquired Pneumonia (HAP) in the Intensive Care Unit (ICU) to Empiric Antibiotics

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Kata kunci:
Antibiotik;
Sensitivitas bakteri;
HAP;
ICU.

ABSTRAK

Terapi utama pengobatan pneumonia adalah antibiotik. Penggunaan antibiotik memerlukan perhatian khusus agar tidak terjadinya resistensi antibiotik. Oleh karena itu, penting untuk mengetahui mikroorganisme patogen penyebab infeksi *hospital acquired pneumonia* (HAP). Penelitian ini bertujuan untuk mengetahui gambaran sensitivitas bakteri gram negatif dan positif terhadap antibiotik empiris pada pasien HAP. Jenis penelitian ini adalah penelitian observasional deskriptif analitik dengan rancangan *cross sectional*. Pengambilan data dari data rekam medik pasien periode Januari 2019 – Desember 2020. Kriteria inklusi adalah pasien ICU diagnosa HAP, usia ≥ 15 tahun, memiliki catatan medis yang lengkap (usia, sputum, leukosit, hasil foto x-ray thorax) riwayat pengobatan, parameter *outcome* (TTV). Kriteria eksklusi yaitu wanita hamil, pulang paksa dan lama perawatan di ICU < 48 jam. Analisis data penelitian ini dilakukan secara deskriptip dan uji Likelihood Ratio. Hasil menunjukkan gambaran sensitivitas bakteri gram positif terhadap antibiotik empiris HAP adalah rifampin (78%), TMP-Sulfametoxazole (78%), vancomicin (100%), linesolid (100%) sedangkan sensitivitas bakteri gram negatif adalah cefaperazole-sulbactam (≥75%), amikasin dan imipenem (≥ 55%) dan sensitivitas antibiotik terhadap bakteri ESLB dan MRSA yaitu memiliki sensitivitas yang sangat rendah (≤ 50%) dan terdapat hubungan yang signifikan antara usia dan tingkat Pendidikan dengan pertumbuhan bakteri pada sputum ($p<0.05$). Kesimpulan penelitian ini adalah Vancomicin dan linesolid sensitif terhadap bakteri gram positif, cefaperazole-sulbactam sensitif terhadap bakteri gram negatif dan sudah terjadi resistensi terhadap bakteri ESLB dan MRSA.

Key word:
Antibiotics;
Bacterial Sensitivity;
HAP;
Intensive Care Unit.

ABSTRACT

Antibiotics are the primary treatment for pneumonia. The use of antibiotics requires special attention to prevent antibiotic resistance. Therefore, it is important to know the pathogenic microorganisms that cause hospital-acquired pneumonia (HAP) infections. This study aimed to describe the sensitivity of negative-positive bacteria to empiric antibiotics in HAP patients. The study method was an analytical descriptive observational study with a cross-sectional design. Data were collected from patient medical records for the period January 2019 – December 2020. Inclusion criteria were ICU patients diagnosed with HAP, aged 15 years, with complete medical records (age, sputum culture, leukocytes, chest x-ray results), treatment history, and outcome parameters (vital signs). Exclusion criteria were pregnant patients, involuntary discharge, and ICU stay of less than 48 hours. The data in this study were analysed descriptively and likelihood ratio. The results of the

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description showed that the empiric antibiotics with sensitivity more than 70% against gram-positive bacteria causing HAP were rifampin (78%), TMP-sulfamethoxazole (78%), vancomycin (100%), and linezolid (100%), while the empiric antibiotics with sensitivity more than 70% against gram-negative bacteria were cefoperazone-sulbactam (≥75%), followed by amikacin and imipenem (≥55%). Meanwhile, the empiric antibiotics had a very low sensitivity (≤ 50%) against ESLB-producing bacteria and MRSA. There is a significant relationship between age and educational level factors and bacterial growth in sputum cultures ($p<0.05$). **Conclusion**: Vancomycin and linezolid are sensitive to gram-positive bacteria, cefoperazone-sulbactam is sensitive to gram-negative bacteria, and resistance to ESLB-producing bacteria and MRSA has occurred.

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INTRODUCTION

Indonesia is a developing country facing health problems, particularly infectious diseases. Infectious diseases have the highest prevalence of any disease category. Lower respiratory tract infections are predicted to kill 2.56 million people worldwide, making it the fourth leading cause of death in the world. In Indonesia, the number is 50,000. (Roth et al., 2018)'(Pranata, 2020)'(WHO, 2019). Pneumonia is a lower respiratory tract infection that causes inflammation of the lung parenchyma, resulting in lung tissue consolidation and impaired gas exchange, leading to in-hospital mortality and morbidity. (Pranata, 2020)'(Wells et al., 2017). In 2018, the prevalence of pneumonia in Indonesia was 2%(Kemenkes RI, 2018). Nosocomial pneumonia or hospital-acquired pneumonia (HAP) occurs 48 hours or more after admission to the hospital which, usually in the intensive care unit (ICU). Bacterial pathogens of HAP and VAP include gram-negative bacteria (*Pseudomonas aeruginos*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Acinetobacter* spp) and gram-positive bacteria (*Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Streptococcus spp)*. Differences in host factors and hospital flora influence the pattern of pathogens causing infections (Shebl & GULIC, 2022).

Pneumonia can affect people all ages, including infants, children, and adults(Febriyana et al., 2023). According to Fitri (2022), the initial treatment for pneumonia is the administration of empiric antibiotics for the first 48-72 hours. In line with this, appropriate empiric antibiotics can reduce the mortality rate of *P.aeruginosa* bacteria(Apriliany et al., 2022). Another study explained that the antibiotics commonly used in the treatment of pneumonia therapy are ceftriaxone (81.5%), cefixime (1.4%), cefotaxime (7.1%), and ampicillin (10%), and the administration of ceftriaxone has shown good efficacy with better outcomes than other antibiotics(Apriliany et al., 2023). One study identified the six types of gram-negative bacteria most commonly found in the ICUs of regional hospitals in Bali, namely *Acinetobacter baumannii*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Escherichia coli,* and *Pseudomonas aeruginosa*, and five bacteria in the multidrug-resistant (MDR) category, namely *A. baumannii*, *E. cloacae*, *E. coli*, *K. pneumoniae* and *P. aeruginosa*. The bacteria *A. baumani* and *E. cloacae* were included in the carbapenem-resistant (CR) and extended-spectrum cephalosporin-resistant (ESCR) categories. The results of this study also showed that *E. coli* bacteria had a significant relationship between antibiotic use and the percentage of bacterial sensitivity in the ICU, and that higher antibiotic use caused a decrease in bacterial sensitivity to antibiotics (p=0.024)(Meriyani, et al., 2021). According to Tran GM, there were three types of bacteria that most commonly caused antibiotic resistance in the ICU in the patients with ventilator-associated pneumonia (VAP) in 2017: *Acinetobacter* (n = 75), *Klebsiella* (n = 39), and *Pseudomonas aeruginosa* (n = 29). *Acinetobacter baumannii* is resistant to ceftazidime, ceftriaxone, piperacillin, imipenem, meropenem, ertapenem, ciprofloxacin, and levofloxacin, while *Klabsiella* is resistant to ceftriaxone and ceftazidime. These data show that sick patients on ventilators are at very high risk of developing antimicrobial resistance. These data also explain that *Acinetobacter*, *Klebsiella* and *Pseudomonas aeruginosa* and other multi-drug resistant bacterial pathogens pose serious therapeutic problems in ICU patients(Tran et al., 2017).

Resistance is emerging rapidly and is a global threat leading treatment failure. Infections caused by MDR bacteria lead to increased mortality and morbidity(Macvane, 2017) . According to the WHO, pneumococcus is one of the bacteria that is of international concern because it causes global antibiotic resistance (WHO, 2020). A study conducted by Ervina (2021) explained the bacteria that caused pneumonia at Dr. M. Goenawan Partowidigdo Pulmonary Disease Hospital was gram-negative bacteria and antibiotics that had a sensitivity of more than 70% in gram-positive bacteria were linezolid, nitrofurantoin, teicoplanin, and vancomycin and in gram-negative bacteria were amikacin, gentamicin, imipenem, meropenem and piperacilin-tazobactam(Ervina et al., 2021). The use of prophylactic antibiotics aims to eradicate and prevent pathogenic bacteria, but the use of these antibiotics carries the risk of causing resistance. This is consistent with a study by Sánchez-Ramírez

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(2018), which discovered that the use of selective antibiotics in the first four days of treatment can increase bacterial resistance(Sánchez-Ramírez et al., 2018). The main treatment for pneumonia is the use of antibiotics. According to Hapsari (2019), the appropriateness of empiric antibiotic treatment for pneumonia with pneumonia therapy guidelines was 43.4%(Hapsari & Kurniawati, 2019). Another study explained that the use of antibiotics has increased by 30% to 80% in developing countries and by 13% to 37% in developed countries(Kemenkes RI, 2015). The use of antibiotics requires special attention to prevent antimicrobial resistance, which is becoming a global problem. This resistance makes it difficult to treat infectious diseases. Treatment becomes expensive when the infection cannot be treated with first-line antibiotics, which in turn affects patient clinical outcomes such as length of stay, increased hospital care costs and increased mortality(WHO, 2020).

Antibiotic resistance in the intensive care unit (ICU) leads to increased length of stay and mortality due to several factors including the use and selection of potent and selective antibiotics(Meriyani, et al., 2021). According to WHO, 2021, antibiotic resistance is a global health problem, and antimicrobial resistance (AMR) data reported that *E. coli* (36.6%) is resistant to third-generation cephalosporins and S. aureus is resistant to methicillin 24,9% (World Health Organization, 2021). A study by Tran GM, 2017, explaind that antibiotic resistance in ICU patients was resistance to ceftriaxone (88%), ceftazidime (80%), ciprofloxacin (77%), cefepime (75%) and levofloxacin (72%)(Tran et al., 2017). Therapeutic management is very important to achieve optimal outcomes. Therefore, it is important to know the pathogenic microorganisms that cause HAP infections. This study expects to contribute or update research for science and clinicians by providing an overview of the bacterial pathogens that cause HAP and assist in the selection of empiric antibiotic therapy. This study aims to determine the sensitivity of gram-negative and gram-positive bacteria to empiric antibiotics in patients with hospital-acquired pneumonia (HAP) in hospitals. The selection of appropriate antibiotics can suppress antibiotic resistance occurrence and support antimicrobial resistance control programs (PPRA) in hospitals, especially West Nusa Tenggara Provincial Hospital, to control antibiotic resistance.

METHODS

Research Design and Sampling Techniques

This study is analytical descriptive observational research with a cross-sectional design. It was conducted from March to May 2021 in West Nusa Tenggara Provincial Hospital in the ICU inpatient facility, and was declared appropriate by the Ethics Committee of the West Nusa Tenggara Provincial Hospital (No: 070/160/0016/RSUDPP NTB). The data were collected from the patients' medical records for the period from January 2019 to December 2020. The population was 1002 cases, while the population of pneumonia patients was 22,477 cases and a population estimate was obtained (1002 ≈ 0.04).

The sample size was calculated with a margin of error of 5% (0.05) and a minimum sample size of 60 patients was obtained (Lemeshow formula). Inclusion criteria were ICU patients with a diagnosis of HAP, aged 15 years or older, with complete medical records (age, laboratory results such as sputum culture, leukocytes, chest x-ray results), treatment history, and outcome parameters (vital signs). Exclusion criteria were pregnant patients, forced discharge, and ICU stay of less than 48 hours.

Data Collection and Analysis

Data collection was based on inclusion and exclusion criteria. Patient demographic data collection included age, sex, admission and discharge dates, antibiotic therapy, sputum culture results, vital signs, leukocytes, chest X-ray results, and treatment history. The criteria for sputum culture that met

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the requirements were polymorphonuclear neutrophilic leukocytes (PMN) found greater than 25 per low-power field and epithelial cells less than 10 per low-power field to see validation.

Percentage of Bacterial Sensitivity

The percentage of bacterial sensitivity to antibiotics was based on the CSLI and Ministry of Health regulations regarding antimicrobial resistance control programs in hospitals. The percentage of sensitivity was calculated as the number of sensitive antibiotics divided by the number of isolates tested for that antibiotic multiplied by one hundred percent. Methicillin-resistant *Staphylococcus* (MRS) sensitivity percentage was calculated as the number of MRS isolates divided by the number of *Staphylococcus* sp isolates plus the number of MRS isolates multiplied by one hundred percent. The percentage sensitivity of ESLB-producing bacteria was calculated as the number of ESLB isolates divided by the number of non-ESLB-producing isolates plus the number of ESLB-producing isolates multiplied by one hundred percent. The percentage sensitivity of ESLB-producing *K. pneumoniae* was calculated as the number of ESLB-producing *K. pneumoniae* isolates divided by the number of non-ESLB-producing *K. pneumoniae* isolates plus the number of ESLB-producing *K. pneumoniae* multiplied by one hundred percent" (Kemenkes RI, 2015).

RESULTS AND DISCUSSION

Factors associated with bacterial culture positivity

Tabel 1. Factors associated with bacterial growth in sputum cultures (N=36)

Demografi	Patients HAP (n=36)	*p*
Sex		
Male	31 (86%)	0,540[a]
Female	5 (14%)	
Age (Years)		
18-60	24 (67%)	0,046[a*]
≥ 61	12 (33%)	
Mean±SD	54,72±12,80	
Leukosit (10^3/mm^3)		
Range	4590-30490	
Mean±SD	18962,22±5641,03	
Respiratory rate		
Range	10-29	0,102[a]
Mean±SD	17,92±6,23	
Temperature (^{0}C)		
Range	35,5-38	0,106[a]
Mean±SD	36,1±0,91	
Body Mass Indexs		
Normal	18 (50%)	0,55[a]
Obeses	14 (39%)	
Underweight	4 (11%)	
Length of hospital stay		
1-7 days	4 (11%)	0,640[a]
>7 days	32 (89%)	
Educational Attainment		
Elementary- High school	24 (67%)	0,01[a*]
College	12 (33%)	

[a]Likelihood Ratio

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This study is a retrospective study conducted in West Nusa Tenggara Regional Public Hospital, and the data were collected using medical records of patients diagnosed with hospital-acquired pneumonia (HAP) in the intensive care unit from January 2019 to December 2020. This study included 106 participants diagnosed with HAP, but after patient screening, the number of participants who fit the inclusion criteria data was 36.

Table 1 shows the factors associated with bacterial growth in sputum cultures. Based on the data in table 1, participants were predominantly male (86%). In this study, male participants had a history of active and passive smoking, which causes a lot of exposure to cigarette smoke pollution. Cigarette smoking is one of the risk factors for the incidence of pneumonia and can suppress the body's immune system. One study stated that the incidence of pneumonia occurred more in men than in women. Several other studies also showed that the incidence of pneumonia occurred mostly in men than in women(Naito et al., 2017),(Liu et al., 2023),(Sitompul et al., 2022). Similar to this study, a study explained that the incidence of pneumonia occurred mostly in men (57.45%) than in women (42.55%) with gram positive bacteria as the cause (Atia et al., 2020). According to a study by Assefa et al (2022), the incidence of pneumonia was associated with cigarette smoking. Cigarette smoking causes decreased immune systems and infections that cause the immune system to not be able to clean or eliminate bacteria causing pneumonia from the lower respiratory tract and alveoli. This causes the bronchioles and alveoli to become filled with inflammatory leukocyte exudate and fluid. Thus, decreased carbon dioxide with oxygen in the lungs occurs and causes symptoms of respiratory disorders such as cough, an increase in sputum, dyspnea, chest pain, and respiratory dysfunction and/or shock in severe cases (Assefa et al., 2022).

The age of the participants in this study was dominated by the age of 18-60 years (67%) with a mean of 54.72±12.80 and p-value of < 0,05. This explains that age was a factor associated with bacterial growth in sputum cultures and most infections occurred in those aged 18 to 60 years. In the study of Akhmad et al (2024), pneumonia mostly occurred in those aged 56 to 65 years (36.6%), and gram-negative bacteria were mostly that caused pneumonia and were mostly found in ICU, cardiovascular ICU, surgical ward, and isolation room(Akhmad et al., 2024). Another research explained that pneumonia mostly occurred in those aged 18 to 60 years (26.28%) and bacteria *Klebsiella pneumonia* mostly caused the infection in adult patients whereas *P.aeruginosa* caused the infection in the elderly with p-value of <0.0001 (Liu et al., 2023). The study by Shodikin (2021) explained that the patients with pneumonia were mostly in the age of 18-65 years (53,2%) with bacterial growth in sputum cultures being *Acinetobacter baumanii* (29%), *Klebsiella pneumonia* (14%), *Entrobacter aerogenes* (14%), *Pseudomonas aeruginosa* (14%), *Burkholderia cepacian* (7%), *Pseudomonas fluorescens* (7%), *Salmonella arizonae* (7%), and *Escherichia coli* (7%) (Shodikin et al., 2021).

Length of hospital stay of patients participating in this study was more than seven days (89%) with mean leukocytes of 18962.22±5641.03, respiratory rate of 17.92±6.23 and temperature 36.1±0.91. The study by Il A'la (2017) explained that pneumonia patients with an average length of stay determined by the Indonesia Diagnosis Related Group (INA-DRG) have a high and significant risk depending on the severity of the pneumonia suffered. This causes the impact of comorbidities and complications of the diseases(Il A'la et al., 2017).

The educational level of the participants in this study was dominated by elementary school, middle school, and high school graduates (67%) with a p-value of 0.05. This indicates that the patients with these educational levels were associated with bacterial growth in sputum cultures and infection. According to Al-Dalfi et al (2023), half of the parents with primary school education had children with pneumonia. Parents with low levels of education have limited knowledge of good hygiene and nutrition, financial barriers to accessing health services, and a lack of awareness of preventive measures such as immunizations. Lack of immunization is also a factor that can increase the risk of pneumonia in children (Al-Dalfi et al., 2023).

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The body mass index (BMI) status of the participants in this study was predominantly classified as normal (50%) and obese (39%). According to the study by Bramley et al (2017), patients with obese BMI status (aOR, 2.1; 95% CI, 1.4–3.2) were more likely to be admitted to the ICU and use a ventilator (aOR, 2.7; 95% CI, 1.3–5.6) and were associated with length of stay in pneumonia patients(Bramley et al., 2017). Body mass index (BMI) significantly strengthened the prognostic performance of NT-proBNP in patients with CAP(Lee et al., 2021). In contrast to this study, other studies have found that malnutrition has an effect on the body's immune system by causing a decrease in the body's immune system, accompanied by an increase in the incidence of infection. Malnutrition causes reduced levels of immunoglobulin concentrations, immunoglobulins actions, interleukin-2 receptors, and T-cell subsets (helper, suppressor, cytotoxic, and natural killer cells) and is significantly associated with symptom severity and a higher proportion of positive sputum cultures(Park et al., 2016). Other studies also found that there was no association between normal and obese BMI status and respiratory inflammation as measured sputum (FMD) cell counts(Todd et al., 2007).

In the ICU, empirical antibiotic therapy is initiated before definitive microbiological results are available. Measuring patient demographics such as age, gender, and education level can help optimize antibiotic selection and improve patient outcomes. Age guides antibiotic choice due to differences in pharmacokinetics and pharmacodynamics. It helps assess the risk of multidrug-resistant (MDR) infections, which are more common in elderly patients. Aids in adjusting dosing, especially in neonates, children, and geriatric populations with altered metabolism and renal clearance. Gender can influence drug metabolism, distribution, and elimination. Females may have different immune responses and side effects from certain antibiotics. Some infections (e.g., Nosocomial pneumonia or hospital-acquired pneumonia (HAP), urinary tract infections) are more common in one gender, impacting empirical treatment choices. More precise empirical antibiotic selection reduces the risk of resistance and inappropriate therapy. Tailoring antibiotics based on age and gender enhances efficacy and minimizes adverse effects. Avoiding unnecessary broad-spectrum antibiotics decreases hospital stay duration and associated costs. Identifying high-risk groups helps implement targeted infection control measures in the ICU. This appropriateness of antibiotics may be due to Educational Attainment having good communication skills in reporting a chief complaint, being aware of health-seeking behavior, and adhering to counseling including antibiotics taking and investigations. Patients who believe that the prescribed antibiotics prevent seriousness use antibiotics more appropriately than those who don`t understand the use of antibiotics. Incorporating demographic data allows a more individualized treatment plan, improving survival rates and recovery speed. Therefore, this study generates valuable data for researchers, policymakers, and prescribers on the appropriateness of antibiotic use and factors at West Nusa Tenggara Provincial Regional Hospital

Data on Gram-Negative and Gram-Positive Bacteria Isolates in the Intensive Care Unit

The isolates of bacteria causing HAP in West Nusa Tenggara Provincial Regional Hospital are presented in Table 2. Samples that met the inclusion criteria required 36 isolates from HAP patients. This number did not reach the minimum number based on the calculation of the number of samples. However, the Clinical and Laboratory Standard Institute (CLSI) states that the minimum number of samples for analysis and presentation of sensitivity data for the minimum number of isolates is 30 isolates(Hindler et al., 2014). Other studies have also stated that the minimum number of isolates tested for analysis and the percentage of sensitivity data is 30 isolates(Akualing & Rejeki, 2016). In this study, 36 isolates of bacteria with the characteristics of pathogens that cause nosocomial pneumonia were obtained: *Staphylococcus haemolyticus*, *Acinobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, methicillin-resistant Staphylococcus (MRS), and extended spectrum beta-lactamase (ESLB) producing bacteria. Figure 1 explains the bacteria causing HAP in West Nusa Tenggara Provincial

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Regional Hospital were gram-negative bacteria (50%) and gram-positive bacteria (50%). A study by Veronica (2018) explains that *Klebsiella pneumoniae* bacteria produces ESLB, which causes resistance to penicillin (Veronika & Kristia, 2018). This study is supported by the study of Ervina (2021) regarding the most common bacteria that cause HAP, namely *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Staphylococcus haemolyticus*(Ervina et al., 2021) (Ervina et al., 2021).

Several other studies also show results consistent with this study, that the bacteria that the most commonly cause nosocomial pneumonia are *Pseudomonas aeruginosa* (24%), *Acinetobacter* spp (16%), and *Acinetobacter baumannii* (12%)(Asadullah et al., 2015). *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* are associated with nosocomial infections, often resulting in multidrug-resistant infections(Geller et al., 2018). Not much different results were also obtained from the study conducted by Kurniawan J et al, (2015) where the three most common bacteria causing HAP were *Klebsiella* sp (47.54%), *Streptococcus α* hemolytic (38.43%), and *Staphylococcus aureus* (12. 50%)(Kurniawan et al., 2015). A study by Klompas (2016) explained that the most common bacteria causing HAP were *S. aureus*, *P. aeruginosa*, Klebsiella species, enterobacter species, and Haemophilus species(Klompas et al., 2017). A study by Atia (2020) explained that the most common bacteria causing pneumonia were *Streptococcus pneumonia* (43,3%), followed by *Pseudomonas aeruginosa* (13,8%), *Staphylococcus aureus* (6,9%), *Escherichia coli* (6,2%), *Entrobacter spp* (4,5%) and *Citrobacter* (2,2%) (Atia, 2020). According to studies, the pathogens that cause nosocomial pneumonia are multi-drug resistant (MDR) bacteria, for example, *S. pneumoniae*, *H. influenzae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* spp, and gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA)(Wells et al., 2017),(Pranata, 2020),(W H O, 2017) .

Table 2. Bacteria causing HAP in West Nusa Tenggara Provincial Regional Hospital for the period January 2019 – December 2020 (N=36)

Name	**Total**	
	n	**%**
Staphylococcus haemolyticus	9	25
Acinobacter baumannii	9	25
Pseudomonas aeruginosa	4	11
Klebsiella pneumonia	3	8
Methicilin resistant staphylococcus sp. (MRS)	9	25
Ekstended spectrum beta-lactamase (ESLB)	2	6
Total	36	100

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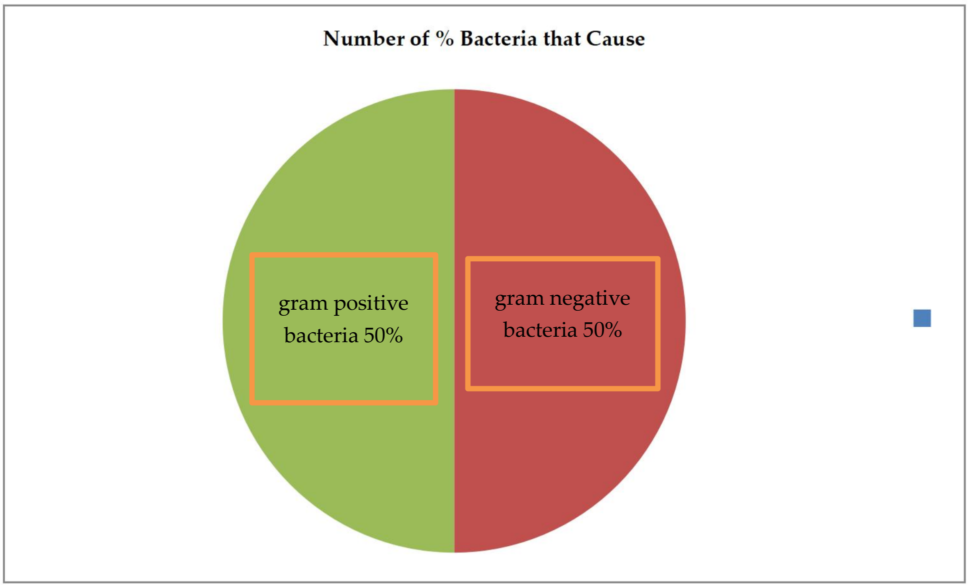

Figure 1. Percentage of bacteria causing HAP in West Nusa Tenggara Provincial Hospital

Description of Sensitivity of Gram-Positive Bacteria.

Figure 2 shows an overview of the sensitivity of gram-positive bacteria causing HAP to empiric antibiotics in West Nusa Tenggara Provincial Regional Hospital. In this study, the antibiotics that had a sensitivity of ≥ 70% were rifampin (78%), TMP-sulfamethoxazole (78%), vancomycin (100%), and linezolid (100%). Vancomycin has a mechanism of action, namely by inhibiting cell wall biosynthesis, and blocking glycopeptide polymerization by binding D-alanyl-D-analine to the cell wall. Vancomycin has been used as an empiric therapy for gram-positive bacteria without a high-risk factor for mortality with an increase in MRSA (methicillin-resistant *Staphylococcus aureus*) and can be administered at a dose of 15 mg/kg IV every 8 hours to 12 hours (loading dose 25-30 mg/kg x 1 for severe illness). Linezolid also works by binding to bacterial rRNA at the 23S of the 50S subunit to prevent the bacterial protein translation process. The dose of linezolid 600 mg IV was given every 12 hours (Kalil et al., 2016),(Grayson, 2018).

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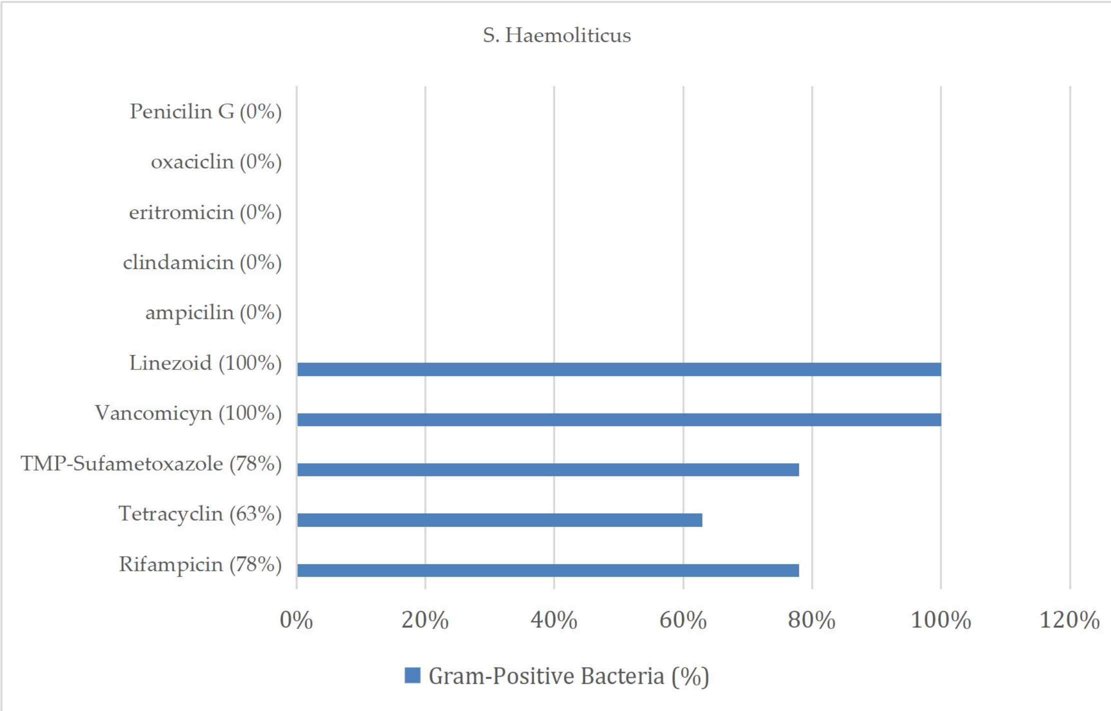

Figure 2. Description of the Sensitivity of Gram-Positive Bacteria that Cause HAP to Empiric Antibiotics in West Nusa Tenggara Provincial Hospitals

Description of Sensitivity of Gram-Negative Bacteria

Figure 3 shows an overview of the sensitivity of gram-negative bacteria causing HAP to empiric antibiotics in West Nusa Tenggara Provincial Regional Hospital. In this study, the antibiotic that had a sensitivity of ≥75% was cefoperazone-sulbactam, followed by those that had a sensitivity of ≥ 55%, which were amikacin and imipenem. The mechanism of cefoperazone-sulbactam is that cefoperazone inhibits the formation of bacterial cell walls, while sulbactam inhibits the beta-lactamase enzyme. Meanwhile, the mechanism of action of imipenem is to inhibit the synthesis of bacterial walls by inhibiting the binding of penicillin to protein walls, which causes lysis/rupture of bacterial cells(Grayson, 2018). According to IDSA (2016), the empiric antibiotic recommendation for HAP is piperacillin+tazobactam at 4.6g IV every 6 hours, imipenem 500 mg IV every 6 hours (Kalil et al., 2016). A study by Ulla (2022) also shows the same thing as this research, namely that ampicillin and co-amoxiclave are resistant to *Klebsiella* at 4.6% and 4.2%. Apart from that, ampicillin is also resistant to *P.aeruginosa* (4.3%) and *E.coli* (3.1%). This research also explains that *Klebsiella* and *P.aeruginosa* are resistant to the cephalosporins (Ullah et al., 2022). Other research explains that *P.aeruginisa* is moderately resistant to the antibiotics ciprofloxacin (24%), gentamicin (24%), and amikacin (23%)(Atia et al., 2020).

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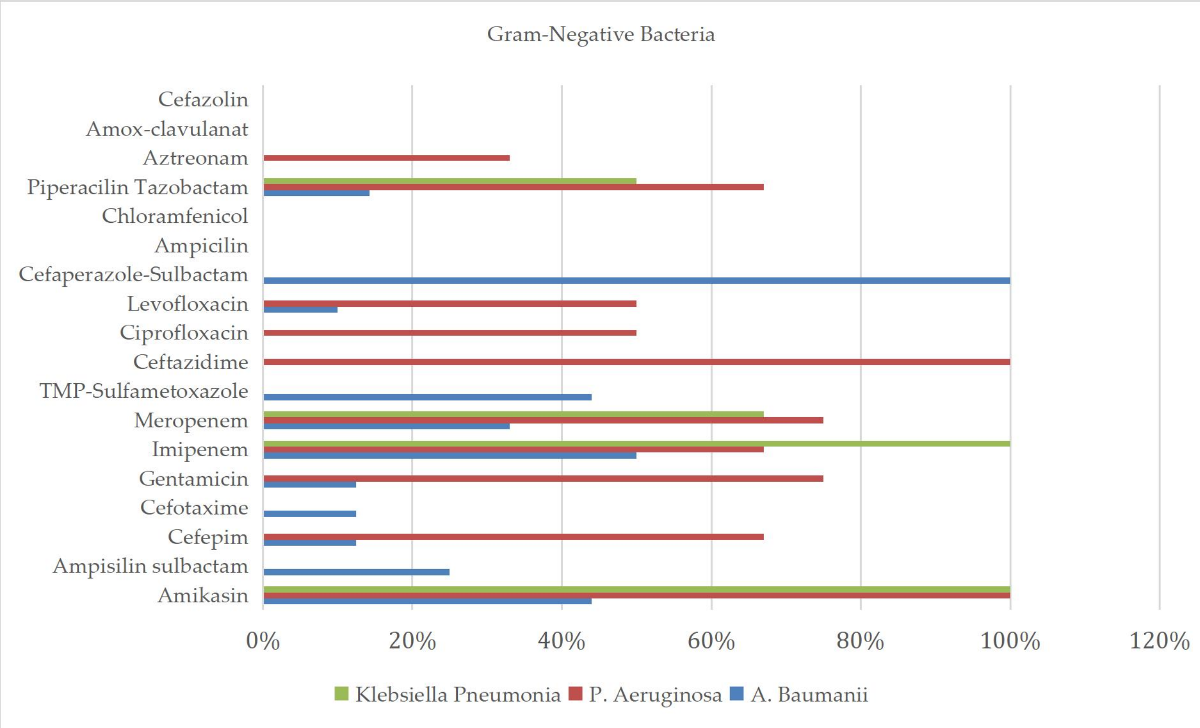

Figure 3. Description of the Sensitivity of Gram-Negative Bacteria Causing HAP to Empiric Antibiotics in West Nusa Tenggara Provincial Hospitals

Description of Sensitivity of MRSA and ESLB-Producing Bacteria

Table 5 describes the sensitivity of antibiotics against ESLB-producing bacteria and MRSA. From this study, the sensitivity data showed that all of the antibiotics tested had very low sensitivities, ≤ 50%, against both ESLB-producing bacteria and MRSA. This explains the resistance exhibited by the bacteria Extended Spectrum Beta-Lactamase (ESLB) producing bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA). Therefore, it is important for West Nusa Tenggara Provincial Regional Hospital to attention to several antibiotics to which ESLB-producing bacteria and MRSA have been tested to be resistant. According to a study by Ziolkowski (2018), based on data from the International Nosocomial Infection Control Consortium (INICC), bacterial resistance in the ICU causes an increase in mortality associated with healthcare-associated infections (HAIs) and non-HAIs, as well as an increase in the length of inpatient treatment (Ziółkowski et al., 2018). There are several causes of antibiotic resistance in the ICU, such as cross-transmission and high antibiotic use. The majority of patients treated in the ICU are patients with severe comorbidities, post-operative patients requiring intensive care, and patients treated with catheters, tracheal tubes, or peripheral venous catheters, which place patients at a high risk for infection and require antibiotic therapy(Pons & Ruiz, 2019). Another study also explained that the causes of antibiotic resistance are poor infection control and inappropriate and excessive use of antibiotics (Popović et al., 2020). A study by Ulla (2022) explained that gentamisin has developed resistance to Klebsiella Pneumonia (3.8%) and P.aeruginosa (2.3%) (Ullah et al., 2022).

Table 5. Description of Sensitivity of ESLB-Producing and MRSA causing HAP to Empiric Antibiotics in West Nusa Tenggara Provincial Regional Hospital

Antibiotics	**ESBL**	***MRSA***	***Klebsiella Pnemonia***	***Staphylococcus haemolyticus***

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	S	N	%	S	N	%	S	N	%	S	N	%
Amikasin	2	5	40				2	5	40			
Imipenem	2	5	40				2	5	40			
Piperacilin-Tazobactam	0	3	0				0	3	0			
Amox-Clavulanat	0	5	0				0	5	0			
Ampicilin	0	5	0	0	18	0	0	5	0	0	18	0
Ampicilin-Sulbactam	0	2	0				0	2	0			
Cefazolin	0	5	0				0	5	0			
Cefepim	0	5	0				0	5	0			
Ciprofloxacin	0	5	0				0	5	0			
Gentamicin	0	5	0				0	5	0			
Levofloxacin	0	5	0				0	5	0			
Meropenem	0	5	0				0	5	0			
TMP-Sulfametoxazole	0	6	0	7	18	39	0	6	0	7	18	39
Tetracixlin-Tazobactam	1	4	25				1	4	25			
Rifampicin				5	18	28				5	18	28
Tetracixlin				5	16	31				5	16	31
Vancomicin				9	18	50				9	18	50
Linezolid				9	18	50				9	18	50
Clindamicin				0	8	0				0	8	0
Eritromicin				0	16	0				0	16	0
Oxacixlin				0	16	0				0	16	0
Penisilin G				0	16	0				0	16	0

S= Sensitivity, N=Number

CONCLUSIONS

The empiric antibiotics with sensitivity greater than or equal to 70% against gram-positive bacteria causing HAP are rifampin (78%), TMP-sulfamethoxazole (78%), vancomycin (100%) and linezolid (100%). Meanwhile, the empiric antibiotics with sensitivity greater than or equal to 75% against gram-negative bacteria are cefaperazole-sulbactam, followed by those with sensitivity greater than or equal to 55%, which are amikacin and imipenem. The empiric antibiotics have a low sensitivity, ≤ 50%, both against ESLB-producing bacteria and MRSA. There is a significant relationship between age and educational level factors and bacterial growth in sputum cultures ($p<0.05$).

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