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Article

Ventilator Associated Pneumonia (VAP) Antibiogram of Dr. Soebandi Hospital, Jember In 2019

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Abstract: *Ventilator-Associated Pneumonia* (VAP) is a type of nosocomial infection that occurs after 48-72 hours of endotracheal intubation with a high mortality rate and is most commonly seen in hospital ICUs The high mortality rate in VAP cases could, among other things, be caused by the emergence of multidrug resistant (MDR) species that may be caused by irrational use of antibiotics. The existence of an antibiogram is expected to solve the problem. This study aimed to form a VAP antibiogram of dr. Soebandi Hospital in Jember City, East Java, Indonesia, can be used to reference rational therapy.This research is a descriptive study using secondary data obtained from medical records. The data will be collected and analyzed in a univariate manner, and then the analysis results will be displayed in graphs and tables. The number of samples used was 37 medical record data that matched the criteria and obtained 39 isolates. Of the 39 isolates, 22 different types of bacteria were obtained. These bacteria come from 7 different families. In addition, of the 39 identified types of bacteria, 29 of them were Gram-negative bacteria (74%), the remaining 10 were Gram-positive bacteria (26%). The antibiotics with the most useful and have a sensitivity level of more than 50% in this study were amikacin (77%), piperacillin-tazobactam (65%), and cephalexin (54%). These three antibiotics are also available in the parenteral form be used as empirical therapy for VAP.

Keywords: Pneumonia, Antibiotics, Antibiogram.

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1. Introduction

Ventilator-Associated Pneumonia (VAP) is one of the most common types of nosocomial infections in hospital ICUs, due to the use of mechanical ventilation so that it is classified as a nosocomial infectious disease with a high mortality rate.[1] This infection usually occurs after 48-72 hours of endotracheal intubation and is characterized by progressive formation of infiltrates accompanied by signs of systemic infection (fever and changes in leukocyte count), detection of infectious agents, and changes in sputum characteristics.[2] It accounts for about half of all patients with hospital-acquired pneumonia cases and is estimated to occur in approximately 9–27% of all mechanically ventilated patients, with the highest risk being in the early stages of hospitalization. This makes VAP the second highest disease due to nosocomial infection in the ICU.[3]

Empiric administration of antibiotics is used as initial management for VAP therapy before the patient's culture. However, empirically inappropriate and excessive administration of antibiotics can aggravate the patient's condition and cause mutations of pathogenic bacteria so that they are resistant to antibiotics.[4] According to the Regulation of the Minister of Health of the Republic of Indonesia number 8 of 2015 regarding the antimicrobial resistance control program in hospitals which was initiated through a comprehensive antimicrobial resistance control movement or called the Antimicrobial Resistance Control Program.[5]

Implementation guidelines also need to be prepared to optimize efforts to control antimicrobial resistance in hospitals throughout, Indonesia. To prevent antimicrobial resistance, the choice of antibiotics must be based on the results of culture and sensitivity tests or based on the germ map and antibiotic sensitivity patterns in the antibiogram at the hospital.(6) Antibiograms can assist doctors in choosing the best empiric antibiotic treatment while waiting for the results of

microbiological culture and sensitivity tests and to assist pharmacists as the main supplier and regulator of medicines.[7]

This antibiotic is also a useful tool for detecting and monitoring the development of bacteria's resistance and sensitivity to antibiotics in hospitals.[8] It is mandatory that antibiograms be produced in a hospital, health care system, or other health care facility (such as quarterly or one year). The development of resistance and bacterial sensitivity to antibiotics can be identified and investigated. This makes antibiograms very important for every health care center. However, until now at RSD dr. Soebandi still does not have a special antibiogram for VAP cases. This study aimed to provide information about *Ventilator Associated Pneumonia* (VAP) antibiogram of dr. Soebandi Hospital, Jember in 2019.

2. Materials and Methods

This research is a descriptive study with a population of VAP cases in RSD Dr. Soebandi in 2019. Sampling was carried out by total sampling method and obtained 37 medical record data following the criteria, namely conducting a culture showing the causative bacteria and antibiotic sensitivity testing. In this study, from 37 patient medical records, there were 39 isolates. The data used are secondary data obtained from the patient's medical record, including initials, age, sex, tested specimens, culture indications, identified bacterial species, and antibiotic sensitivity test results. The data will be collected and analyzed univariately to determine the sample's characteristics. Then the analysis results will be displayed in graphs and tables based on sensitive (S), medium (I), and resistance (R). The ethical approval was granted under the number 1453/H25.1.11/KE/2021 from the Faculty of Medicine, University of Jember.

3. Results

In this study, a total of 37 medical records of VAP patients who performed culture were used, and antibiotic sensitivity tests were used as the research sample. There were 27 male patients (73%) and ten female patients (27%). Based on the age group, the age interval with the highest culture rate was in the age interval 45-65 years, namely 11 patients (30%). The characteristic of the subjects can be seen in Table 1.

Table 1. Distribution of sex and age of the study sample

Variables	Category	Number	Percentage
Sex	Male	27	73%
	Female	10	27%
Age	<17	5	13%
	17-25	8	22%
	25-45	8	22%
	45-65	11	30%
	>65	5	13%

All bacteria identified were 22 different types of bacteria, as shown in Table 2. These bacteria come from 7 different families. Besides, of the 39 identified types of bacteria, 29 of them were Gram-negative bacteria (74%), the remaining 10 were Gram-positive bacteria (26%).

Table 2. Distribution of bacterial types resulting from culture

Gram	Family	Species	Frequency	Percentage
Gram-Negative	*Enterobacteriaceae*	*K. pneumonia*	5	13%
29 Isolates		*K. ornithinolytica*	1	3%
74%		*K. oxytoca*	1	3%
		E. aerogenes	2	5%
		E. cloacae	1	3%
		Enterobacter spp	1	3%
		E. coli	2	5%
		S. orizonae	1	3%
	Moraxellaceae	*A. baumanii*	4	10%
	Morganellaceae	*P. mirabilis*	1	3%
	Pseudomonadaceae	*C. luteola*	1	3%
		C. freundii	1	3%
		P. aeruginosa	5	13%
		P. fluorescens	1	3%
		P. oryzihabitans	1	3%
	Burkholderiaceae	*B. cepacia*	1	3%
Gram-Positive	*Micrococcaceae*	*K. varians*	4	10%
10 Isolates		*Micrococcuss spp*	1	3%
26%	*Staphylococcaceae*	*S. capitis*	1	3%
		S. haemolyticus	1	3%
		S. lentus	1	3%
		Streptococcus sp	2	5%
		Total	39	100%

Gram-negative bacteria were dominated by *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (13%), *Acinetobacter baumanii* (10%). *Enterobacter aerogenes* and *Escherichia coli* were found in two isolates, respectively. Meanwhile, *Klebsiella ornithinolytica, Klebsiella oxytoca, Enterobacter cloacae, Enterobacter spp, Salmonella orizonae, Proteus mirabilis, Chryseomonas luteola, Citrobacter freundii, Pseudomonas fluorescens, Pseudomonas oryzihabitans, Burkholderia cepacia* each were found. A total of 10 identified Gram-positive bacteria were dominated by *Kocuria varians*, namely four isolates (10%). Followed by *Streptococcus sp*. namely two isolates (5%) and four other isolates found the growth of bacteria *Micrococcus spp, Staphylococcus capitis, Staphylococcus haemolyticus*, and *Staphylococcus lentus*, namely one isolate each. The results of the 5 most bacterial sensitivity tests to antibiotics are shown in Table 3.

Table 3. The results of the sensitivity test for the most 5 bacteria to antibiotics

Spesies Bakteri	ATM	AMC	AZM	AMP	AK	CXM	C	CFR	DA	CIP	KZ	CN	CFP	CFM	CTX	CAZ	CRO	DO	E	FOX	GM	IPM	K	LEV	LZD	MEM	P	SAM	SXT	TOB	TE	TIC	TZP	OX	OFX	VA	KF	FOS	CPM	CT
Bakteri Gram Negatif																																								
K. pneumoniae (n=5)	R	R	-	-	S	R	-	-	-	-	-	-	-	-	R	I	-	-	S	-	R	-	-	I	-	-	-	-	R	-	S	S	-	S	-	-	-	-	-	-
	S	S	-	R	S	S	S	-	-	S	I	-	-	S	S	S	S	-	-	S	S	-	S	S	-	S	-	S	S	S	S	-	S	-	-	-	-	S	-
	R	R	-	R	S	R	R	-	-	I	R	R	-	-	R	R	-	-	-	R	-	I	R	S	-	-	-	R	R	I	R	-	S	-	-	-	-	-	-
	R	R	-	R	S	R	S	-	-	S	R	S	-	-	R	R	-	-	-	I	-	S	R	S	-	-	-	R	R	R	-	-	S	-	-	-	-	-	-
	R	R	-	R	S	R	R	-	-	I	R	R	-	-	R	R	-	-	-	S	-	I	R	I	-	-	-	R	R	S	R	-	R	-	-	-	-	-	-
A. baumanii (n=4)	-	-	-	-	R	-	-	-	-	R	-	R	-	-	R	R	-	R	-	-	-	-	-	R	-	-	-	R	R	R	R	-	R	-	-	-	-	-	-
	-	-	-	-	R	-	-	-	-	R	-	R	-	-	R	R	-	R	-	-	-	-	-	-	R	-	-	-	R	S	R	R	-	R	-	-	-	-	-
	-	-	S	-	-	-	S	-	R	R	-	R	-	-	-	-	-	I	I	-	R	-	-	-	R	R	-	R	-	R	-	R	-	-	-	R	-	-	-
	-	-	-	-	S	-	R	-	-	R	-	S	-	R	R	R	R	I	-	-	-	-	-	R	-	S	-	S	R	S	R	-	I	-	-	-	-	-	-
P. aeruginosa (n=5)	S	-	-	-	S	-	-	-	-	S	-	S	-	R	S	S	-	-	-	-	-	-	-	S	-	I	-	-	-	S	-	S	S	-	-	-	-	-	-
	-	R	-	R	S	R	-	R	-	S	-	S	-	R	R	S	-	R	-	-	-	-	-	S	-	S	-	R	R	-	R	-	S	-	-	-	-	-	-
	S	-	-	-	S	-	-	-	-	S	-	S	-	-	S	S	-	-	-	-	-	S	-	S	-	-	-	-	-	S	-	I	S	-	-	-	-	-	-
	R	-	-	-	S	-	-	-	-	R	-	R	-	-	R	R	-	-	-	-	-	S	-	R	-	-	-	-	-	R	-	R	R	-	-	-	-	-	-
	I	-	-	-	S	-	-	-	-	S	-	S	-	-	S	S	-	-	-	-	-	S	-	S	-	-	-	-	-	S	-	I	S	-	-	-	-	-	-
Bakteri Gram Positif																																							
K.varians (n=4)	-	R	R	R	-	-	R	R	R	R	-	-	-	R	-	-	-	R	-	R	-	-	-	R	R	R	-	-	S	-	R	-	-	R	-	R	-	-	-	-
	-	R	S	R	-	-	R	R	R	-	-	-	-	R	-	-	-	S	-	R	-	-	-	S	-	S	-	-	S	-	R	-	-	R	-	R	-	-	-	-
	-	I	S	R	-	-	-	R	-	S	-	-	-	R	-	-	-	S	R	R	-	-	-	S	-	S	-	-	S	-	S	-	-	R	-	R	-	-	-	-
	-	R	R	R	-	R	R	R	R	-	-	-	-	-	-	-	-	R	-	R	-	-	-	-	R	R	-	-	S	-	-	-	-	R	-	R	-	-	-	-
Streptococcus sp (n=2)	-	I	S	R	-	-	R	R	R	S	-	-	-	R	-	-	-	S	R	R	-	-	-	S	R	S	-	-	S	-	-	-	-	R	-	R	-	-	-	-
	-	R	R	R	-	-	R	R	R	R	-	-	-	R	-	-	-	R	-	R	-	-	-	R	-	S	-	-	S	-	R	-	-	R	-	R	-	-	-	-

ATM = aztreonam, AMC = amoxicillin-clavulanic acid, AZM = azithromycin, AMP = ampicillin, AK = amikacin, CXM = cefuroxime, C = chloramphenicol, CFR = cefadroxyl, DA = clindamycin, CIP = ciprofloxacin, KZ = cephalexin, CN = cephalexin , CFP = cefoperazone, CFM = cefixime, CTX = cefotaxime, CAZ = ceftazidime, CRO = ceftriaxone, DO = doxycycline, E = erythromycin, FOX = cefoxitin, GM = gentamicin, IPM = imipenem, Kacin = kanamycin, LEV = levoflox = linezolid, MEM = meropenem, P = penicillin, SAM = ampicillin-sulbactam, SXT = cotrimoxasol, TOB = tobramycin, TE = tetracycline, TIC = ticarcycline, TZP = piperacillin-

tazobactam, OX = oxacillin, OFX = ofloxacin, VA = vancomycin . KF = cephalotin, FOS = phosphomycin, CPM = cefepime, CT = colistine, S = sensitive, I = intermediate, R = resistant.

4. Discussions

The isolates obtained from this study were 39 isolates. This is because there were two patients underwent culture examinations and antibiotic sensitivity tests two times. This 2-time examination aims to confirm the type of bacteria that causes VAP in patients and to determine the pattern of sensitivity to antibiotics. Several things can cause the failure to re-examine all samples, for example, the cost constraints incurred are greater or the patient's clinical condition has improved.[9] *Klebsiella pneumoniae* is the nosocomial pathogen that most commonly causes VAP and accounts for 10% of all hospital-acquired infections. These bacteria also cause other infections such as meningitis, septicemia, and purulent abscesses. In previous studies, it was known that 7-12% of nosocomial pneumonia in intensive care units in the United States was caused by *Klebsiella pneumonia*.[10]

Pseudomonas aeruginosa is also one of the most frequently cause VAP, with a prevalence of around 4% and resulting mortality as high as 13.5%, even with adequate antibiotic treatment. The serotype of *Pseudomonas aeruginosa* that causes VAP can vary. Serotypes O6 and O11 are the most common and are associated with a clinical resolution of 60%. Meanwhile, serotypes O1 and O2 are less common strains but have higher mortality. In MDR strains, mortality rates can increase by up to 35.8%. The presence of an MDR strain have been identified as an independent predictor of hospital mortality (with an odds ratio of 1.634 and a confidence interval of 95%).[11]

Kocuria varians is the most common Gram-positive bacteria found. These bacteria are highly aerobic and were previously classified into the genus *Micrococcus* but have now been differentiated from *Micrococcus* based on the phylogenetic and chemotaxonomic analysis. These bacterial clusters are generally considered non-pathogenic commensals that colonize the skin, mucosa, and oropharynx. However, they can be opportunistic pathogens in immunocompromised patients, despite infection cases.[12] The second most common Gram positive bacteria that cause VAP are *Streptococcus sp.* Biofilm formation in the endotracheal tube (ETT) is a common phenomenon that can provide a bacterial reservoir for VAP in mechanically ventilated patients.

Previous studies have reported that *Pseudomonas sp.* and *Enterobacter sp.* is a common pathogen that causes VAP. However, it was also identified in the ETT biofilm of patients without VAP, suggesting that *Pseudomonas sp.* and *Enterobacter sp.* in ETT a biofilm is required but not sufficient to cause VAP. Oral bacterial species are considered as potential reservoirs of pathogens involved in VAP. In this study, it was also known that the number of *Streptococcus sp* in the ETT biofilm was significantly associated with the incidence of VAP.(13) Other Gram-positive bacteria that can cause VAP and that have been identified from this study include *Micrococcus sp, Staphylococcus capitis, Staphylococcus haemolyticus,* and *Staphylococcus lentus.*

The antibiotics most frequently tested on more than 50% of identified bacteria include aztreonam (ATM), amoxicillin-clavulanic acid (AMC), ampicillin (AMP), amikacin (AK), chloramphenicol (C), ciprofloxacin (CIP), cephalexin. (CN), cefotaxime (CTX), ceftazidime (CAZ), cefoxitin (FOX), levofloxacin (LEV), ampicillin-sulbactam (SAM), cotrimoxazole (SXT), tobramycin (TOB), tetracycline (TE), and piperacillin-tazobactam (TZP). Antibiotics were tested against 50% of bacteria found, there are only three antibiotics with a sensitivity level of more than 50%, among others: amikacin (AK) (77%), piperacillin-tazobactam (TZP) (65%), and cephalexin (CN) (54%).

Antibiotics with resistance levels include: ampicillin (AMP) (90%), cefoxitin (FOX) (74%), cefotaxime (CTX) (73%), ampicillin-sulbactam (SAM) (70%), tetracycline (TE) (66.7%), aztreonam (ATM) (66.6%), chloramphenicol (C) (64.3%), amoxicillin-clavulanic acid, (AMC) (62.5%), ceftazidime (CAZ) (54%), tobramycin (TOB) (54%), ciprofloxacin (CIP) (50%). This study's results are also following previous research at the Harapan Kita Hospital Jakarta, which states that the antibiotic amikacin shows high sensitivity to the main causes of VAP so that it can be used as first-line therapy in VAP cases.[14]

In another study, a bacterial pattern based on VAP onset was also presented, with culture isolates stratified by day of sampling. Early-onset VAP cases were collected on hospitalization days 1–4, and late-onset VAP cases were retrieved on hospital days five or later. The most dominant early-onset VAP was *Pseudomonas aeruginosa*, with the highest antibiotic amikacin sensitivity. In late-onset VAP, the most prevalent was *Pseudomonas sp,* followed by *Pseudomonas aeruginosa* with the highest sensitivity pattern to *Pseudomonas sp* and *Pseudomonas aeruginosa* was to amikacin.

However, a study conducted at the ICU Fatmawati Hospital on the relationship between empiric antibiotic use and bacterial sensitivity in the ICU Fatmawati Hospital Jakarta showed that almost all bacteria were resistant to cephalexin (> 75%). This can be caused by the bacteria that cause VAP at RSD dr. Soebandi is more sensitive to cephalexin antibiotics than bacteria identified in the

ICU Fatmawati Hospital Jakarta.[15] In several journals, it was also stated that piperacillin-tazobactam antibiotics were the most widely used antibiotics (63%), followed by the fluoroquinolones (57%), vancomycin (47%), cephalosporins (28%) and aminoglycosides (25%).(16) Amikacin, piperacillin-tazobactam, and cephalexin can be administered parenterally, so all three can be used as VAP therapy.

5. Conclusion

This study showed that the most beneficial antibiotics with a sensitivity level of more than 50% for VAP patients were amikacin (77%), piperacillin-tazobactam (65%), and cephalexin (54%). These three antibiotics are also available in parenteral form for use as empirical therapy for VAP.

Conflicts of Interest

The authors 'don't have any conflict of interest.

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