

## ORIGINAL RESEARCH

## Bacterial and sensitivity pattern of pathogens causing Ventilator-Associated Pneumonia in Intensive Care Unit

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### ABSTRACT

**Background:** Ventilator-Associated Pneumonia (VAP) is the most common nosocomial infection in Intensive Care Unit (ICU). Antimicrobial resistant bacteria isolated from VAP patients are often associated with high mortality and length of hospital stay. **Objective:** This study aimed to analyze the pattern and sensitivity among pathogens that caused VAP in ICU. **Materials and Methods:** The study was conducted retrospectively by extracting the data of bacterial isolates from sputum specimens in the Laboratory of Clinical Microbiology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia and confirming the clinical data on patients suffering from VAP in ICU ward. The study started from January until December 2017. **Results:** The total 148 pathogens were isolated, 18 of them were diagnosed as VAP, and 130 were not VAP. The most predominant isolates in the VAP group were *Acinetobacter baumannii* as many as 38 (9%) followed by *Pseudomonas aeruginosa* 22 (2%), *E. coli* 16 (7%), and *Klebsiella pneumoniae* 11 (1%). The pathogens showed a sensitivity rate above 70% to cefoperazone-sulbactam (SCF), meropenem (MEM) and amikacin (AK). Mortality in VAP patients was 33.3% and the VAP group had a longer hospital stay compared to non-VAP group. **Conclusion:** The three most predominant bacteria that were found were *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*. The pathogens had sensitivity rate above 70% to cefoperazone-sulbactam, meropenem, and amikacin.

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## BACKGROUND

Intensive care unit (ICU) admissions are common among severely-ill hospitalized patients. Most of the time, it is necessary for ICU patients due to their underlying disease and condition to be intubated and ventilated. Even though it is crucial for patients with respiratory problems to use mechanical

ventilators, these devices could potentially damage anatomical barriers, cough reflex, and mucociliary clearance of patients' respiratory tract, thus impairing their lower respiratory track's defense mechanism (Kalanuria, et al., 2014). This condition could weaken the current compromised patient's immune system and make the patients more prone to nosocomial infections, commonly ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) was defined by 2016 American Thoracic Society guideline as an onset of pneumonia occurring more than 48 hours after endotracheal intubation (Kalil, et al., 2016). Clinical signs of VAP consist of new lung infiltrations, signs of systemic infection, change in the sputum characteristics, and causative agent findings (Kalanuria, et al., 2014). According to the latest NHSN surveillance guide, diagnosis of VAP now focuses more on the culture findings of causative pathogens. VAP was classified as probable and possible VAP according to its cultural findings, whether it is qualitative or quantitative culture evidence (Spalding & Minshall, 2020). Based on the onset, VAP was divided into two groups: early-onset VAP and late-onset VAP. Early-onset VAP was stated as VAP that is acquired within the first 4 days after intubation. VAP occurring more than 5 days after intubation was categorized as late-onset VAP. Late-onset VAP is most likely caused by antibiotic-resistant bacteria (Ali, et al., 2015).

VAP is the most common infection that has been found in patients with mechanical ventilators in ICU. The incidence of VAP in Europe was considerably higher, approximately 42.7% in the ICU (Koulenti, et al., 2017). Meanwhile, in the US, 39% of pneumonia patients were VAP (Centers for Disease Control and Prevention, 2014). Considering these high incidences of VAP, adequate empirical antibiotics must be given to those patients. Antibiotic-resistant bacteria will increase, if inadequate empirical therapy was administered. Hence, this will lead to increases in mortality rate, length of hospital to stay, and hospital cost for VAP patients.

## OBJECTIVE

This study aimed to assess bacterial and sensitivity patterns among pathogens that caused VAP isolated from ICU patients so that adequate empirical antibiotic treatment could be established.

## MATERIALS AND METHODS

A retrospective study was performed by collecting the bacterial sensitivity data from ICU patients admitted to Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January until December 2017. This study was approved by a local ethics committee. The samples were collected by recording all sputum isolates from ICU patients diagnosed with VAP. Data about ICU patients and their sputum isolate were excerpted from the Laboratory of Clinical Microbiology Department log book. The patient details such as age, sex, sputum isolates results, antibiotic susceptibility testing results were recorded and analyzed. The patient's outcome and length of hospital stay were excerpted from ICU's files. It was also recorded and analyzed. Antibiotic susceptibility testing was performed using the Phoenix™ Automated Microbiology System machine. Statistical analysis was performed using SPSS software.

## RESULTS

From January until December 2017, a total of 148 isolated pathogens from ICU patients' sputum were recorded. Only 18 out of ICU patients were diagnosed with VAP. Thus, the incidence of VAP among patients with positive sputum culture in this study was 12.2%. The demographic distribution of the VAP incidence was summarized in Table 1. Based on gender, 38.9% of them were male and 61.1% were female. The incidence of VAP was mostly found in the age group 21 to 40 years old (38.95%). Meanwhile, the least common age group were patients among 0 to 20 years old (16.7%). Mortality among VAP patients was moderately high with 33.3%. The mean length of hospital stay is 18.1 days with a minimum length of 4 days and a maximum of 44 days.

Table 1. Demographic distribution

Parameter	Group	Prevalence n (%)
Gender	Male	7 (38.9%)
	Female	11 (61.1%)
Age	0 – 20	3 (16.7%)
	21 – 40	7 (38.9%)
	41 – 60	4 (22.2%)
	61 – 80	4 (22.2%)
Mortality	Deceased	6 (33.3%)
	Alive	12 (66.7%)
Length of stay (days)	Minimum	4
	Maximum	44
	Standard deviation	11.5
	Mean	18.1
Total		18 (100%)

Source: research data, processed

Table 2 shows the isolated pathogens among VAP patients in the ICU from January until December 2017. The pathogens were dominated by gram-negative bacteria. The most isolated pathogens were *A. baumannii* with 38.9%, followed by *P. aeruginosa* (22.2%), *E. coli* (16.7%), and *K. pneumoniae* (11.1%) consecutively. All of *E. coli* isolates were found to be extended-spectrum beta-lactamase (ESBL) positive. Most of the *K. pneumoniae* isolates were also found ESBL positive.

Table 2. Isolated bacteria (n=18)

Bacteria	VAP	
	n (%)	ESBL n (%)
<i>Acinetobacter baumannii</i>	7 (38.9%)	-
<i>Pseudomonas aeruginosa</i>	4 (22.2%)	-
<i>Escherichia coli</i>	3 (16.7%)	3 (100%)
<i>Klebsiella pneumoniae</i>	2 (11.1%)	1 (50%)
<i>Pseudomonas putida</i>	1 (5.6%)	-
<i>Proteus mirabilis</i>	1 (5.6%)	-
Total	18 (100%)	

Source: research data, processed.

Table 3 reveals the overall antibiotic sensitivity pattern of those isolated pathogens. SCF, MEM, and AK were sensitive towards isolated pathogens with more than 60% susceptibility as shown in Figure 1. Most of the pathogens were found sensitive to SCF (83.3%), AK (66.7%) and MEM (61.1%) However, only a few pathogens were found sensitive to CRO (5.8%) and AMP (5.6%). Multidrug resistant (MDR) bacteria were found in overall isolated pathogens.

Table 3. Antibiotic Sensitivity Pattern

Antibiotic	Susceptible (%)
SCF	83.3
AK	66.7
MEM	61.1
TOB	61.1
LEV	58.8
CN	56.3
FEP	52.9
CIP	52.9
CAZ	44.4
SXT	44.4
FOS	40
ATM	38.9
SAM	33.3
FOX	31.3
ETP	27.8
C	23.5
CTX	12.5
TE	12.5

KZ	11.8
AMC	11.1
CRO	5.8
AMP	5.6

Source: research data, processed

**Note:** AMC= Amoxicillin-clavulanic acid; CAZ= Ceftazidime; CTX= Cefotaxime; CRO= Ceftriaxone; FEP= Cefepime; SCF= Cefoperazone-sulbactam; SAM= Ampicillin-sulbactam; MEM= Meropenem; LEV= Levofloxacin; CIP= Ciprofloxacin; AK= Amikacin; FOS= Fosfomycin; FOX= Cefoxitin; SXT= Trimethoprim-sulfamethoxazole; TOB= Tobramycin; AMP= Ampicillin; CN= Gentamicin; ATM= Aztreonam; TE= Tetracycline; C= Chloramphenicol; KZ= Cefazolin; ETP= Ertapenem

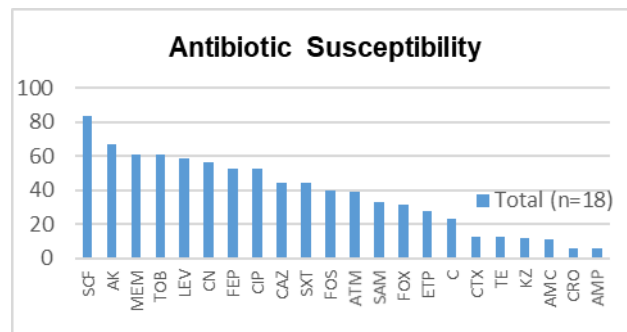


Figure 1. Antibiotic Sensitivity Pattern

## DISCUSSION

### Characteristics of Research Subjects

In our study, the incidence of VAP was more common in females rather than males. However, the previous study stated that the incidence was found more in males compared in females (Golia, et al., 2013; Ergul, et al., 2017). Despite these differences, there has not been any study that proves a significant correlation between gender and VAP incidence, it was causative agent, and it was antibiotic sensitivity results. The incidence of VAP in this study was most commonly found in the age group of 21 to 40 years old, which was similar to the study conducted in Bangalore, India (Golia, et al., 2013). This proves that this age group was more prone to nosocomial infection, in this case, VAP, compared to another age group in this study.

The mortality rate that was found in this study was moderate. Alive cases among VAP patients were considerably high. According to a previous study, VAP patients infected by antibiotic-resistant pathogens were found to have a longer hospital stay. This might be the result of inadequate empirical antibiotic treatment (Zilberberg, et al., 2017). The results regarding mortality rate and length of hospital stay, and its significance with VAP incidence and causative pathogens varied between conducted studies. These variations might be caused by other factors affecting the patient’s outcome, for example, the patient’s underlying disease, the severity of illness, and the patient’s condition when entering ICU.

### The bacterial pattern among isolates

Gram-negative bacteria were predominant in this study. This finding was similar to the results of studies conducted in Jakarta, India, Turkey, Poland, and Iran (Radji, et al., 2011; Golia, et al., 2013; Ergul, et al., 2017; Walaszek, et al., 2018). *A. baumannii* was the most common pathogen isolated in this study, which was similar to studies conducted in Poland and Iran (Walaszek, et al., 2018; Bozorgmehr, et al., 2017). However, a previous study that was also performed in ICU Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in 2013 showed a different result, stating *P. aeruginosa* as the most common pathogens isolated among VAP patients (Tyas, et al., 2013). This proved there was a significant change in bacterial pattern causing VAP in ICU Dr. Soetomo General Academic Hospital, Surabaya, Indonesia within the past years. Several studies conducted in other countries declared *P. aeruginosa* as the most common pathogens isolated among VAP patients (Radji, et al., 2011; Golia, et al., 2013; Ergul et al., 2017). Even though there were varying studies results reported regarding pathogens, those three bacteria were the most common as similar as this study

(Radji, et al., 2011; Golia, et al., 2013; Ergul, et al., 2017; Walaszek, et al., 2018; Bozorgmehr, et al., 2017)

According to Saroj in his study conducted in Bangalore, India, the most common pathogens causing late-onset VAP was *A. baumannii*. In addition, *P. aeruginosa*, *E. coli*, and *K. pneumoniae* were commonly found in both early-onset and late-onset VAP (Golia, et al., 2013). A study from Italy reported the prognosis of VAP patients caused by varying pathogens did not differ from one another, but this result still needs to be considered, regarding the fact that there are a lot of factors affecting patient's prognosis that has not been assessed yet in the study (Marianna, et al., 2012).

### Sensitivity pattern among isolates

As shown in Table 3, antibiotics that have high sensitivity among pathogens in this study were SCF, MEM, and AK. SCF has the highest sensitivity compared to other antibiotics. SCF's sensitivity towards *A. baumannii* was proven in a study in China that tested its efficacy towards extensive drug-resistant (XDR)- *A. baumannii* (Qin, et al., 2018). In this study, AK was highly sensitive towards isolated pathogens, which was similar to previously performed studies (Radji, et al., 2011; Ergul, et al., 2017). MEM was also found considerably sensitive. These findings were in concordance with studies conducted before (Radji, et al., 2011; Walaszek, et al., 2018). Other studies stated that AK and MEM were effective in treating multidrug-resistant gram-negative bacteria and in improving patients' clinical conditions (Ammar & Abdalla, 2018).

In this study, the multidrug-resistant incidence was found. MDR- *A. baumannii* were also found in studies conducted before (Golia, et al., 2013; Ergul, et al., 2017; Nowak, et al., 2017; Walaszek, et al., 2018). AMP was found highly resistant to isolated pathogens. These findings were similar to studies conducted in Jakarta and Poland (Radji, et al., 2011; Walaszek, et al., 2018). In a study performed in a tertiary hospital in India, most of *K. pneumoniae* isolates were multidrug-resistant with a high mortality rate (Patil & Patil, 2017). However, in this study, *P. aeruginosa* was the most common MDR pathogens in isolates. The previous study in Jakarta and India showed the same result (Radji, et al., 2011; Golia, et al., 2013). According to Table 3, overall isolated pathogens were less sensitive to AMP and CRO, compared to other antibiotics. The same results were also found in a study in China (Zhang, et al., 2013).

### Empiric therapy recommendation

The sensitivity and resistance pattern that was found among studies were never identical to one another. The sensitivity pattern of isolated pathogens depends on the type of ICU, antibiotic use in certain ICU, and history of antibiotic use of each VAP patient. In this study, a significant amount of MDR bacteria were found. Resistance of bacteria was caused by the lack of monitoring and standardized use of antibiotics in Indonesia, especially over-the-counter products, and the lack of new antibiotics discovery (Ventola, 2015).

Therefore, an empirical antibiotic therapy strategy based on existing data was needed. Adequate empirical treatment was proven effective not only to reduce mortality rate, hospital cost, length of stay, but also to improve patient's prognosis, and limit excessive use of antibiotics in the ICU ward (Awad et al., 2018). The empirical antibiotic strategy that was based on existing surveillance data could prevent MDR- bacteria incidence that was commonly found in late-onset VAP. According to this study, SCF (cefoperazone-sulbactam) was the most sensitive antibiotic towards isolated pathogens, therefore SCF will most likely be effective against VAP by giving broad-spectrum protection against causative agents, although the effectiveness of SCF as an empiric antibiotic against VAP needs to be proven in further studies.

This study was not conducted without any limitations. One of the limitations that could influence this study was the retrospective design that depends on the completion of patient's data in the hospital. The small sample size in this study was also a factor. Despite these limitations, most of the references used in this study were also using a retrospective design, making the result of this study acceptable. The empirical treatment recommendation was most likely to be used locally in Indonesia, but this limitation only highlights the importance of performing local surveillance routinely, and retrospective data was the easiest instrument to be used in performing surveillance, particularly in the ICU ward.

## CONCLUSION

The most predominant bacteria that were found were *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and *E. coli*. SCF, MEM, and AK were found highly effective against said predominant bacteria. SCF was the most sensitive antibiotic compared to others. The mortality rate of VAP patients was 33.3% with a mean length of hospital stay of 18.1 days. Based on the data of this study, the recommended empirical therapy was cefoperazone-sulbactam (SCF). For adequate empirical therapy, routine local surveillance needs to be performed. To produce valid local surveillance data, a complete, systematic patient report was crucial.

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