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Original Article

Distribution and antibacterial susceptibility pattern of isolated bacteria from endotracheal aspirates among ventilator-assisted pneumonia patients in Indonesia

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Abstract

An accurate and timely identification of causative microorganisms as well as determination of their antibiotic susceptibility patterns will help in the selection of proper antibiotics and prevention of their misuse in pneumonia patients. The aim of this study was to determine the distribution and antibiotic susceptibility pattern of bacteria isolated from endotracheal aspirates of ventilator-assisted pneumonia patients in Indonesia. A retrospective cross-sectional study was conducted at Dr. Zainoel Abidin Hospital, a provincial reference hospital in Banda Aceh, Indonesia, from January to December 2021. Ventilator-assisted pneumonia patients aged ≥17 years treated in the hospital were considered eligible. Antibiotic susceptibility was valuated using Kirby-Bauer disc-diffusion followed with VITEK 2 Compact. We included 57 patients of which 73.7% males and 26.3% aged 56–65 years (represent the majority group of the patients). Each patient reported at least one comorbidity and the average duration of receiving mechanical ventilation was 8.68 days, and more than half (59.7%) of the patients had a poor clinical outcome (died). A total 57 bacteria isolates (consisting nine species) were recovered; 68.5% Gram-negative and 31.5% Gram-positive bacteria. Among 57 patients, *Acinetobacter baumannii* was the most frequent isolated Gram-negative bacteria (19.3%), followed by *Klebsiella pneumoniae* (17.5%), *Pseudomonas aeruginosa* (15.8%), and *Achromobacter denitrificans* (12.3%). *A. baumannii* exhibited <70% sensitivity to aminoglycoside and carbapenem antibiotics and 100% resistance to third-generation cephalosporins. The most abundant Gram-positive bacteria was *Staphylococcus aureus* (17.5%), followed by *S. haemolyticus* (10.5%) and *S. epidermidis* (3.5%). All *S. aureus* were sensitive to linezolid, tigecycline, vancomycin, and macrolide antibiotics (azithromycin, clarithromycin, clindamycin, and erythromycin), whereas 50% were sensitive to some beta-lactams. However, 50% of *S. aureus* were methicillin resistant *S. aureus* (MRSA). Given the magnitude of multi-drug resistance, an empiric antimicrobial therapy in particular to specific settings and implementation of antibiotic stewardship programs are crucial.

Keywords: Endotracheal aspirate, mechanical ventilator, pneumonia, susceptibility pattern, antibiotic resistance

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Received: March 7, 2023 - Accepted: April 27, 2023 - Published online: April 29, 2023

Introduction

The use of invasive medical devices to monitor or to support the patient life such as a mechanical ventilator, has increased patient vulnerability to nosocomial infections [1]. The hospital-acquired infection has been associated with an increased rate of morbidity, mortality, and prolonged hospital stay [2]. Pneumonia is the most common nosocomial infection among hospitalized patients, and those treated in the intensive care unit (ICU) on ventilators are at 2-12 times higher risk of developing nosocomial pneumonia [3-5]. Hospital-acquired pneumonia has been reported to account for more than half of the total infection cases in ICU [3], as well as the leading cause of mortality in this setting [6-8].

Pneumonia approximately occurs in 5–10 out of 1000 hospitalized patients, and the number increases by 6–20 times among those receiving mechanical ventilation [1, 5]. A study reported a 5–67% incidence of ventilator-associated pneumonia (VAP) cases, and the incidence vary based on the country, setting, and diagnostic approach employed [3]. VAP-related mortality has been reported to reach 50%, and the percentage increased to 76% when it came to infections by multidrug-resistant (MDR) microorganisms [9]. A study at Dr. Zainoel Abidin Hospital, Banda Aceh in 2014 reported that 17 patients (48.5%) developed VAP during the period of three months staying in the hospital, with a mortality rate of 23.5% [10].

Appropriate use of antibiotics could reduce mortality rates by up to 46% [11]. Accurate and timely identification of pathogenic microorganisms as well as their susceptibility pattern has been shown to reduce mortality in various infection cases [12]. However, until today, information regarding the distribution and susceptibility pattern of bacteria isolated from VAP patients is limited, giving a challenge not only for proper antimicrobial selection but also for the prevention of its misuse. Meanwhile, irrational use of broad-spectrum antibiotics increases the incidence of antibiotic resistance, which has been considered the leading cause of treatment failure, resulting in an increased length of hospital stay, hospital expense, and mortality rate [13, 14]. Different geographical areas, hospitals, ICU setup, and time of investigation may yield different organisms and their susceptibility patterns [15]. Therefore, knowledge regarding the distribution and antibiotic susceptibility pattern of VAP-related organisms should be well studied and updated. This study aimed to determine the patterns and antimicrobial susceptibility of bacteria isolated from endotracheal aspirate of ventilator-assisted pneumonia patients at Dr. Zainoel Abidin Hospital, a provincial reference hospital in Banda Aceh, the westernmost part of Indonesia.

Methods

Study population, design and setting

A cross-sectional study conducted ventilator-assisted pneumonia patients at Dr. Zainoel Abidin Hospital, Banda Aceh from January to December 2021. A total sampling technique was used of which ICU hospitalized patients aged ≥17 years, diagnosed with pneumonia, receiving mechanical ventilation were considered eligible. Endotracheal aspirates were cultured and antibiotic susceptibility was tested. VAP is the occurrence of pneumonia after at least 48 hours of ventilation. In this study, it was not known exactly the onset time of pneumonia related to ventilator installation.

Patients' general characteristics (age and gender) and clinical profiles (comorbidities, duration of ventilation, and outcomes), as well as the distribution and antibiotic susceptibility profiles of endotracheal aspirate isolates were collected. All positive bacterial cultures were recorded and their susceptibility pattern toward antibiotics was determined.

Isolation and identification of endotracheal aspirate isolates

The endotracheal aspirate specimens, collected with all aseptic precautions using a 50-cm and 12FR suction catheter (introduced through the endotracheal tube of 12–26 cm), were proceeded by mechanically qualifying and homogenizing using a vortex for 1 min. A total of 10 µL of the sample was inoculated onto blood agar and MacConkey agar and were aerobically incubated

overnight at 35±2°C. A 104 colony-forming unit (CFU)/mL was considered as threshold for confirmed diagnosis of pneumonia [16]. All the bacteria were identified by colony morphology, Gram's staining, and relevant biochemical assays.

Antibiotic susceptibility assay

VITEK® 2 Compact (Biomeriux, Lyon, France) was used for further identification of bacteria as well as for antibiotic susceptibility testing. Briefly, pure bacterial colonies obtained from clinical samples were suspended in 0.45% NaCl solution, achieving a density equivalent to McFarland's Standard 0.5, and then were inoculated onto the appropriate cassettes based on Gram staining results, Gram-negative or Gram-positive, for identification and antibiotic susceptibility testing. Bacterial sensitivity and resistance were then determined according to the CSLI guidelines [17].

Statistical analysis

No specific statistical analysis employed in this study. The data were presented as percentage (%), mean ± standard deviation (SD), and median (min-max) as appropriate.

Results

General characteristics of patients

In total, 57 patients were included comprising 42 (73.7%) males and 15 (26.3%) females. The characteristics and clinical profiles of the patients are presented in **Table 1**. Most of the patients aged between 56–65 years (26.3%). All the patients had at least one comorbidity; however, 12.3% of them reported possessing up to 4 comorbidities. The most common comorbidity was cardiovascular disorder (38.6%), followed by chronic kidney disease and anemia (35.1% each), endocrinology disorder (22.8%), and respiratory disorder (7.0%). The average duration of the patients receiving mechanical ventilation was 8.68 days, with a maximum duration of 39 days. More than half of patients (59.6%) had a poor clinical outcome (died).

Table 1. General characteristics and clinical profiles of ventilator-assisted pneumonia patients included in the study (n=57)

Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	42	73.7
Female	15	26.3
Age (years), mean ± SD	47.19 ± 14.51	
17–25	6	10.5
26–35	10	17.5
36–45	9	15.8
46–55	13	22.8
56–65	15	26.3
>65	4	7.0
Comorbidity		
Cardiovascular disorder	22	38.6
Kidney disease	20	35.1
Anemia	20	35.1
Endocrinology disorder	13	22.8
Respiratory disorder	4	7.0
Number of comorbidities		
1	20	35.1
2	22	38.6
3	8	14.0
4	7	12.3
Duration of being on ventilators, mean±SD	8.68±6.48	
Outcomes		
Recovered	23	40.4
Death	34	59.6

Bacterial distribution and antibiotic susceptibility patterns

The distribution of isolated bacteria is presented in **Table 2**. A total of 57 bacteria isolates (consisting nine species) were recovered from 57 endotracheal aspirates; 39 (68.5%) Gram-negative and 18 (31.5%) Gram-positive bacteria. *Acinetobacter baumannii* represented the highest number of Gram-negative bacteria (19.3%), followed by *Klebsiella pneumoniae* (17.5%), *Pseudomonas aeruginosa* (15.8%), and *Achromobacter denitrificans* (12.3%). *Escherichia coli* and *Enterobacter aerogenes* (1.8% each) were the least common Gram-negative bacteria. The most abundant Gram-positive bacteria was *Staphylococcus aureus* (17.5%), followed by *S. haemolyticus* (10.5%) and *S. epidermidis* (3.5%).

Table 2. Distribution of the bacteria isolated from endotracheal aspirate specimens of ventilator-assisted pneumonia patients (n=57)

Bacterial species	Frequency (n)	Percentage (%)
Gram-negative	39	68.5
Acinetobacter baumannii	11	19.3
Klebsiella pneumoniae	10	17.5
Pseudomonas aeruginosa	9	15.8
Achromobacter denitrificans	7	12.3
Escherichia coli	1	1.8
Enterobacter aerogenes	1	1.8
Gram-positive	18	31.5
Staphylococcus aureus	10	17.5
Staphylococcus haemolyticus	6	10.5
Staphylococcus epidermidis	2	3.5
Total	57	100.0

Antibiotic susceptibility patterns of Gram-negative bacteria isolated in this study are presented in **Table 3**. Among the 11 isolated *A. baumannii*, less than 70% were sensitive to aminoglycosides, including amikacin (63.6%), gentamycin (9.1%), and tobramycin (4.1%). However, all *A. baumannii* were found resistant to piperacillin and third-generation cephalosporins (ceftazidime, ceftriaxone and cefotaxime).

Among the ten isolated *K. pneumoniae*, nine (90.0%) were sensitive to amikacin and eight (80.0%) to some carbapenems (doripenem, imipenem, and meropenem) as well as third-generation cephalosporin (cefoperazone). However, all of *K. pneumoniae* isolates were ampicillin and amoxicillin resistant. As expected, *P. aeruginosa* were all (100%) resistant to cefotaxime and sensitive to most beta-lactam and polypeptide antibiotics. *A. baumannii*, *E. coli* and *E. aerogenes* were 100% resistant to third-generation cephalosporins but sensitive to the other tested antibiotics.

All the isolated Gram-positive bacteria were sensitive to linezolid and tigecycline, but resistant to cefixime (**Table 4**). Of the ten isolated *S. aureus*, all were also sensitive to nitrofurantoin, rifampicin, vancomycin, and macrolide antibiotics (azithromycin, clarithromycin, clindamycin and erythromycin), whereas five (50%) were sensitive to beta-lactam (amoxicillin, cefoperazone, ceftriaxone, cefotaxime, ceftizoxime, cefepime, imipenem, meropenem, oxacillin, ampicillin, and piperacillin) and quinolone (ciprofloxacin and levofloxacin) antibiotics.

A total of 50% *S. aureus* were methicillin resistant *S. aureus* (MRSA). All *S. haemolyticus* (100%) were notably resistant to more than 80% of the tested antibiotics, including those of the beta-lactam; however, five (83.3%) were sensitive to vancomycin and three (50%) to rifampicin (**Table 4**). *S. epidermidis* were all (100%) resistant to almost 66% of the tested antibiotics and were sensitive to most macrolide antibiotics, doxycycline, nitrofurantoin, rifampicin, tigecycline, and vancomycin (**Table 4**).

Table 3. Antimicrobial-susceptibility patterns of Gram-negative isolates to different antibiotics

Antibiotic	*Acinetobacter baumannii* (n=11)	*Klebsiella pneumoniae* (n=10)	*Pseudomonas aeruginosa* (n=9)	*Achromobacter denitrificans* (n=7)	*Escherichia coli* (n=1)	*Enterobacter aerogenes* (n=1)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ampicillin	-	10 (100) ‡	-	-	1 (100.0) ‡	1 (100.0) ‡
Amoxicillin/ clavulanic acid	-	6 (60.0) *	-	-	1 (100.0) ***	1 (100.0) ‡
Amoxicillin	-	10 (100) ‡	-	-	-	1 (100.0) ‡
Amikacin	7 (63.6) *	9 (90.0) ***	9 (100.0) ***	7 (100.0) ‡	1 (100.0) ***	1 (100.0) ***
Ceftazidime	11 (100.0) ‡	6 (60.0) *	9 (100.0) ***	5/6 (83.3) **	1 (100.0) ‡	1 (100.0) ‡
Ceftriaxone	11 (100.0) ‡	2 (20.0) *	-	7 (100.0) ‡	1 (100.0) ‡	1 (100.0) ‡
Cefotaxime	11 (100.0) ‡	2 (20.0) *	9 (100.0) ‡	7 (100.0) ‡	1 (100.0) ‡	1 (100.0) ‡
Doxycycline	3 (27.3) *	7 (70.0) **	-	4 (57.1) *	1 (100.0) ***	1 (100.0) ***
Doripenem	1 (9.1) *	8 (80.0) **	8 (88.9) **	-	1 (100.0) ***	1 (100.0) ***
Cefoxitin	-	8 (80.0) **	-	-	1 (100.0) ***	1 (100.0) ‡
Gentamycin	1 (9.1) *	5 (50.0) *	9 (100.0) ***	2 (28.6) *	1 (100.0) ***	1 (100.0) ***
Imipenem	1 (9.1) *	8 (80.0) **	9 (100.0) ***	7 (100.0) ***	1 (100.0) ***	1 (100.0) ***
Levofloxacin	1 (9.1) *	6 (60.0) *	8 (88.9) **	7 (100.0) ‡	1 (100.0) ‡	1 (100.0) ***
Meropenem	1 (9.1) *	8 (80.0) **	9 (100.0) ***	3/6 (50.0) *	1 (100.0) ***	1 (100.0) ***
Polymyxin B	10 (90.9) ***	-	9 (100.0) ***	-	-	-
Cefoperazone/ sulbactam	3 (27.3) *	8 (80.0) **	9 (100.0) ***	7 (100.0) ‡	1 (100.0) ***	1 (100.0) ***
Tobramycin	4 (36.4) *	7 (70.0) **	9 (100.0) ***	5 (71.4) **	1 (100.0) ‡	1 (100.0) ***
Piperacillin/ tazobactam	11 (100.0) ‡	7 (70.0) **	7/8 (87.5) **	7 (100.0) ***	1 (100.0) ***	1 (100.0) ***

‡ Resistant
*<70% of isolates are susceptible
** 70–90% of isolates are susceptible
*** ≥ 90% of isolates are susceptible
- Intrinsic resistance

Table 4. Antimicrobial-susceptibility pattern of Gram-positive isolates to different antibiotics

Antibiotics	*Staphylococcus aureus* (n=10)	*Staphylococcus haemolyticus* (n=6)	*Staphylococcus epidermidis* (n=2)
	n (%)	n (%)	n (%)
Amoxicillin/clavulanic acid	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Amoxicillin	1 (10.0) *	6 (100.0) ‡	2 (100.0) ‡
Azithromycin	10 (100.0) ***	6 (100.0) ‡	2 (100.0) ***
Cefixime	5/5 (100.0) ‡	6 (100.0) ‡	2 (100.0) ‡
Cefoperazone	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Ciprofloxacin	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Clarithromycin	10 (100.0) ***	6 (100.0) ‡	2 (100.0) ***
Clindamycin	10 (100.0) ***	2 (33.3) *	2 (100.0) ‡
Ceftriaxone	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Cefotaxime	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Ceftizoxime	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Doxycycline	7/7 (100.0) ***	-	2 (100.0) ***
Erythromycin	10 (100.0) ***	6 (100.0) ‡	2 (100.0) ***
Cefepime	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Cefoxitin	1/6 (17.0) *	6 (100.0) ‡	2 (100.0) ‡
Nitrofurantoin	10 (100.0) ***	6 (100.0) ‡	2 (100.0) ***
Imipenem	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Levofloxacin	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Linezolid	10 (100.0) ***	6 (100.0) ***	2 (100.0) ***
Methicillin	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Meropenem	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Oxacillin	5 (50.0) *	6 (100.0) ‡	2 (100.0) ***
Piperacillin	1 (10.00) *	6 (100.0) ‡	2 (100.0) ‡
Rifampicin	10 (100.0) ***	3 (50.0) *	2 (100.0) ***
Ampicillin/sulbactam	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Tigecycline	10 (100.0) ***	5/5 (100.0) ***	2 (100.0) ***
Ticarcillin	1 (10.0) *	6 (100.0) ‡	2 (100.0) ‡
Piperacillin/tazobactam	5 (50.0) *	6 (100.0) ‡	2 (100.0) ‡
Vancomycin	10 (100) ***	5 (83.3) **	2 (100.0) ***

‡ Resistant
*<70% of isolates are susceptible
** 70–90% of isolates are susceptible
*** ≥ 90% of isolates are susceptible
- Intrinsic resistance

Discussion

A mechanical ventilator is an important and widely used medical device among patients in ICU [18]. However, utilization of such endotracheal tubes increases the risk of infections such as VAP, which contributes to a high rate of ICU-associated morbidity and mortality [8]. Studying the prevalence and susceptibility patterns of responsible microorganisms will help in the selection of appropriate antibiotics for successful treatment. In the present study, all bacteria isolates from endotracheal aspirates of mechanically ventilated-assisted pneumonia patients were analyzed.

Similar to that reported in previous studies [19, 20], males accounted for more than half (73.7%) of the total VAP patients in this study. In addition to a higher prevalence of the smoking habit among males [21, 22], reproductive hormones such as testosterone and estrogen have been linked to a greater prevalence of males developing VAP [4]. Testosterone tends to reduce the body's immune response to infectious agents, while estrogen increases the intensity and number of immune cells [21]. Higher estradiol levels in women allow for better protection against pathogens [4, 21, 23]. In terms of age, the group of 56–65 years represented the highest percentage (26.3%), which was in line with the finding a previous study (mean age 58.5 ± 19.4 years) [24]. Age has been considered one of the independent risk factors for pneumonia among

ventilator users [25, 26]. This is because physiological functions of the respiratory system, respiratory muscle atrophy, and elasticity of lung tissue decrease with an increase in age [4]. Furthermore, along with aging, people will have a decline in immune responses and tend to possess the comorbidity. The majority of the patients in the present study indeed reported 2 comorbidities (38.6%), including cardiovascular diseases, kidney diseases, and anemia, which are evidenced as risk factors for pneumonia [11, 27].

Of the total 57 isolates obtained from 57 endotracheal aspirate specimens of which Gram-positive accounted for 31.5% and Gram-negative for 68.5% (**Table 2**). This finding is comparable to those of other studies, where Gram-negative bacteria were found to be more prevalent [28, 29]. Gram-negative organisms have been reported as the main cause of ICU-associated infections across Asian-Pacific countries [9, 30]. The most commonly isolated Gram-negative bacteria in our study (*A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*) are in line with previous systematic review [31]. These organisms have been identified as the main causative bacteria of infections among ventilator users in different ICUs in Indonesia [6, 32].

Pathogenicity of *A. baumannii* and *P. aeruginosa* has been reportedly associated with their ability to form biofilm on invasive medical devices including medical ventilators [33-35], increasing the risk of pneumonia among mechanically ventilated patients. *A. baumannii* often infect males, the elderly, and people with chronic diseases such as kidney disease and diabetes [36]. Similar to *A. baumannii*, *K. pneumoniae* infection also commonly occurs in the elderly and people with immunocompromise, and its pathogenicity is often attributed to its hypervirulence, multi-antibiotic resistance, and metastatic spread [36].

All *A. baumannii* were multidrug-resistant (ceftazidime, ceftriaxone, cefotaxime, and tobramycin). This percentage was higher compared to 63.4%–77.6% reported multi-drug resistant *A. baumannii* by the previous study [37]. We also found that the *A. baumannii* were 90.9% sensitive to polymyxin B, 63.6% to amikacin, and <40% to other tested antibiotics (**Table 3**), which was lower than that reported previously (74.9% sensitive for amikacin and 62.7% for meropenem) [38]. To develop its resistance, several mechanisms, such as the production of β-lactamases, increment of multidrug efflux pumps, reduction in membrane permeability, and alteration in the target site of antibiotics have been reported [38].

K. pneumonia in the present study was all (100%) resistant to the group of penicillin (ampicillin and amoxicillin) and was most sensitive to amikacin (90.0%). In a previous study [39], *K. pneumonia* was sensitive to amoxicillin and resistant to ampicillin. We also observed lower *K. pneumonia* sensitivity rates to cephalosporin antibiotics (ceftazidime: 60.0% and cefotaxime: 20.0%) as compared to those reported by Huang *et al.* in Shanghai tertiary hospital (ceftazidime: 96.7% and cefotaxime: 93.3%) [9].

In this study, all the 9 (100%) isolated *P. aeruginosa* were resistant to cefotaxime. Its high rate of resistance (90.0%) to cefotaxime has also been reported previously [35]. In contrast with a previous study that reported *P. aeruginosa* resistance to imipenem (20.8%), ceftriaxone (85.0%), gentamicin (71.9%), and levofloxacin (32.0%) [35], our study recorded 100% sensitivity of *P. aeruginosa* to all the aforementioned antibiotics, along with other several aminoglycoside, beta-lactam, and polypeptide antibiotics.

All *S. aureus* were sensitive to azithromycin, clarithromycin, clindamycin, erythromycin, nitrofurantoin, rifampicin, linezolid, tigecycline, and vancomycin, whereas 50% were identified as MRSA. Other studies also found that 100% of isolated *S. aureus* were sensitive to linezolid [40, 41]. *S. aureus* also showed different levels of sensitivity (10–50%) to other tested antibiotics, mainly beta-lactam, in this study. In contrast, *S. aureus* obtained from a hospital ICU in Jambi, Indonesia was notably resistant to nitrofurantoin [42].

There are some limitations of this study that need to be discussed. We could not confirm that all the pneumonia patients included in this study were VAP cases. To be able to confirm as VAP, the pneumonia should occur after at least 48 hours of ventilation while in this study it was not exactly known whether the onset of pneumonia occurred after the ventilator installation. The responsible mechanisms related to the resistance are not determined in this study. Detection of the presence of resistance-associated genes will benefit to understand the possible

antibiotic resistance mechanisms among ventilator-assisted pneumonia patients in the westernmost part of Indonesia archipelago in the future.

Conclusions

A total of nine species of bacteria were isolated from 57 among ventilator-assisted pneumonia patients of which predominantly was Gram-negative bacteria. *A. baumannii* and *S. aureus* were the most commonly isolated Gram-negative and Gram-positive bacteria, respectively. *A. baumannii* showed low sensitivity to aminoglycoside and carbapenem, and were resistant to some of third-generation cephalosporin antibiotics. *S. aureus*, on the other hand, were found sensitive to almost all beta-lactams, vancomycin, and linezolid. The antibiotic cefixime was found resistant for all Gram-positive organisms. These data indicate high magnitude of antibiotic resistance in ventilator-assisted pneumonia patients and implementation of antibiotic stewardship programs are therefore crucial to be implemented.

Ethics approval

Ethical approval was obtained from the Ethical Committee of Faculty of Medicine, Universitas Syiah Kuala Banda Aceh, Indonesia (016/ETIK-RSUDZA/2022).

Acknowledgments

Authors would like to thank all the staff at Microbiology Laboratory of Dr. Zainoel Abidin Hospital Banda Aceh, Indonesia for their assistance during the study.

Conflict of interest

The authors declare no conflict of interest.

Funding

The study received no external funding.

Underlying data

All data underlying the results can be requested from the corresponding author.

How to cite

Andayani N, Mahdani W, Nisyra M, Agustin H. Distribution and antibacterial susceptibility pattern of isolated bacteria from endotracheal aspirates among ventilator-assisted pneumonia patients in Indonesia. Narra J 2023; 3(1): e149 - http://doi.org/10.52225/narra.v3i1.149.

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