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Risk Factors for Extended Spectrum Beta-Lactamase Producing *Klebsiella pneumoniae* in Arifin Achmad Hospital Riau, Indonesia

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Abstract

Multidrug-Resistant (MDR) bacteria that produce Extended-Spectrum Beta-Lactamase (ESBL) isolates pose a global threat to human health, including in Indonesia. The availability of therapeutic options for ESBL-producing *Klebsiella pneumoniae* (ESBL-KP) is limited, making early recognition of patients with ESBL crucial to preventing the spread of these bacteria within the hospital. This study aimed to examine the risk factors associated with ESBL-KP in the Arifin Achmad General Hospital Riau, Indonesia. This prospective case-control study was performed from January to March 2018, with the diagnosis of ESBL established using the Vitek 2 compact automated tool. The risk factors examined were gender, age, specimen type, ward of origin, hospitalization exceeding seven days, history of antibiotic usage, presence of diabetes mellitus, chronic kidney disease, immunocompromised status, ICU care, and hospitalization within the past month. Patients hospitalized for more than seven days were 4.75 times more likely to develop ESBL-KP, while immunocompromised patients were 2.92 times more likely to develop ESBL-KP. However, the history of antibiotic use, diabetes mellitus, chronic kidney disease, ICU care, and hospitalization within the past month did not exhibit statistically significant associations with ESBL-KP infection. Therefore, ESBL-KP infection should be anticipated in patients hospitalized for more than seven days and those who are immunocompromised. It is crucial to implement infection prevention and control measures, as well as selecting appropriate antibiotic therapy.

Keywords: Extended-Spectrum Beta-Lactamase (ESBL), *Klebsiella pneumoniae,* risk factors

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative rod-shaped bacteria that is facultatively anaerobic and non-motile. It is considered an opportunistic pathogen and is known to cause nosocomial infections, including pneumonia, bacteremia, and urinary tract infections.[1] Extended-Spectrum Beta-Lactamase (ESBL) is an enzyme produced by bacteria, including *K. pneumoniae* and *Escherichia coli*, that has the ability to hydrolyze penicillin, first, second, and third-generation cephalosporins, fluoroquinolones, and aztreonam, with the exception of cephamycin and carbapenems. The genes responsible for ESBL production are located in plasmids, allowing for easy transfer and dissemination of resistance.[2]

The emerging Multidrug-Resistant (MDR) ESBL-producing bacterial isolates pose a global threat to human health, including in Indonesia.[3,4] The prevalence of ESBL-producing *K. pneumoniae* (ESBL-KP) varies worldwide. A study conducted in North India by Vijayaanthi et al. in 2013 reported that out of 72 culture samples, ten bacteria tested positive for ESBL, with 60% identified as *K. pneumonia*.[5] In Nepal, a study found that 16% of 145 isolated *K. pneumoniae* strains were ESBL producers.[6] Another study conducted by Anggraini et al. at Arifin Achmad Hospital in Riau, Indonesia, reported a prevalence of 66% for ESBL-KP.[7]

Several studies have identified risk factors associated with ESBL-KP infections, including the use of invasive devices, prolonged hospitalization, antibiotic usage exceeding seven days, diabetes mellitus, and recent hospitalization within the past month.[8,9,10,11] However, research on ESBL-

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producing organisms and their risk factors in Indonesia remains limited.[4] Due to the limited therapeutic options available for ESBL-KP infections, early identification of patients with ESBL is crucial to preventing the spread of these bacteria within the hospital setting.[12] Therefore, the objective of this study is to analyze the risk factors for ESBL-KP at the Arifin Achmad Hospital in Riau Province.

Methods

A prospective case-control study design was employed for this research. Cases were defined as patients who were infected with ESBL-KP, while controls consisted of patients infected with non-ESBL-KP at the Arifin Achmad Hospital, Riau Province, during the period of January to March 2018. The comparison between controls and cases was set at a ratio of 1:1, with a total of 50 samples in each group. The quota sampling technique was utilized to select the samples.[13] The inclusion criteria for control and case groups were patients with complete data, i.e., patient's identity, patient's history and examination result, diagnosis, antibiotic usage, duration of hospitalization, specimen type, ward, medical record number and culture result of ESBL-KP positive or negative. The exclusion criteria was incomplete patient data. The diagnosis of ESBL was confirmed using the Vitek 2 compact (Biomerieux, Marci-l'Etoile, France) automated machine at the Laboratory of Microbiology of the Arifin Achmad Hospital, Riau Province.

The risk factors investigated in this study encompassed gender, age, specimen type, ward of origin, duration of hospitalization exceeding seven days, history of antibiotic usage, presence of diabetes mellitus, chronic kidney disease, immunocompromised status, ICU care, and hospitalization within the past month. To establish the relationship between these risk factors and the incidence of ESBL infection, a chi-square analysis was conducted with a confidence level of 95% (α=0.05). The study protocol received ethical approval from the Ethics Unit of the Faculty of Medicine, Universitas Riau, with number 463/UN.19.5.1.1.8/UEPKK/2017.

Results

Table 1 presents the characteristics of patients in both groups. In the ESBL-KP group, 50% were men, whereas in the non-ESBL-KP group, 56% were men. The highest proportion of patients in both groups fell into the age range of 46-55 years, accounting for 24% and 32%, respectively. Pus specimens constituted the majority in the ESBL-KP group (62%), while sputum specimens were more prevalent in the non-ESBL-KP group (44%). The ESBL-KP group was primarily treated in the surgical ward (38%), whereas the non-ESBL-KP group received treatment in the medical ward (38%). Malignancy was the primary diagnosis in the ESBL-KP group (30%), whereas the non-ESBL-KP group mainly had an infection (30%).

The statistical analysis revealed that hospitalizations exceeding seven days and immunocompromised status increased the risk of ESBL-KP. Hospitalization for more than seven days raised the risk of ESBL-KP by 4.75 times [odds ratio (OR)=4.45; p=0.000]. Immunocompromised patients were 2.9 times more likely to develop ESBL-KP (OR=2.9; p=0.000). Additionally, the results of the statistical tests demonstrated a significant correlation between hospitalizations exceeding seven days and ESBL-producing *K. pneumoniae* (p=0.012) (Table 2). On the other hand, the history of antibiotic use, diabetes mellitus, chronic kidney disease, ICU care, and hospitalization within the past month did not exhibit a statistically significant association with ESBL-KP infection (Table 2).

Discussion

In this study, a comprehensive analysis of potential risk factors associated with ESBL-KP infection was conducted. The findings indicated that hospitalization for more than seven days significantly influenced the incidence of ESBL-producing *K. pneumoniae*. Patients hospitalized for more than seven days had a 4.75 times higher risk of developing ESBL-KP, which is consistent with the results of previous studies.[9,10,14] This suggests that ESBL-KP in Arifin Achmad Regional Hospital, Riau Province, may be acquired during hospital stays due to prolonged exposure to the hospital environment.

Immunocompromised patients with conditions such as malignancy, HIV/AIDS, pulmonary tuberculosis, and immune system disorders had a 2.92 times higher risk of developing ESBL-KP infection. Similar findings were reported in a study conducted in China, which found that cancer patients had a 2.28 times higher risk of developing ESBL-KP.[11] Additionally, a study in North Africa by Buys et al.[15] demonstrated a correlation between HIV

Table 1 Characteristics of Patients Based on Gender, Age, Specimen Type, Ward, and Primary Diagnosis

Variable	ESBL Producing K. pneumoniae (n=50) (%)	ESBL Non-Producing K. pneumoniae (n=50) (%)
Gender		
Male	25 (50)	22 (44)
Female	25 (50)	28 (56)
Age (years old)		
0–5	6 (12)	6 (12)
6–11	2 (4)	0 (0)
12–16	3 (6)	0 (0)
17–25	3 (6)	5 (10)
26–35	6 (12)	5 (10)
36–45	7 (14)	5 (10)
46–55	12 (24)	16 (32)
56–65	6 (12)	8 (16)
>65	5 (10)	5 (10)
Type of specimens		
Sputum	14 (28)	22 (44)
Pus	31 (62)	16 (32)
Blood	1 (2)	5 (10)
Urine	2 (4)	4 (8)
Network	2 (4)	0 (0)
Others	0 (0)	3 (6)
Wards		
Intensive Care Unit	5 (10)	10 (20)
Neonatal Intensice Care Unit (NICU)	0 (0)	1 (2)
Peadiatric Intensive Care Unit (PICU)	6 (12)	1 (2)
Fetomaternal ward	2 (4)	3 (6)
Medical ward	10 (20)	19 (38)
Surgical ward	19 (38)	6 (12)
Mix medical-surgical ward	8 (16)	10 (20)
Primary diagnosis		
Malignancy	15 (30)	3 (6)
Infection	8 (16)	15 (30)
Trauma	14 (28)	7 (14)
Degenerative	5 (10)	12 (24)
Metabolic	5 (10)	10 (20)
Immune system disorder	3 (6)	3 (6)

Table 2 Correlation Between Risk Factors and ESBL Producing *K. pneumoniae*

Variable	ESBL Producing *K. pneumoniae* (n=50) (%)	ESBL Non-Producing *K. pneumoniae* (n=50) (%)	p	OR*
Hospitalization for >7 days				
Yes	30 (60)	12 (24)	0.000	4.75
No	20 (40)	38 (76)		
Antibiotic Usage History				
Yes	44 (88)	44 (88)	1.000	1.00
No	6 (12)	6 (12)		
Diabetes mellitus				
Yes	24 (48)	26 (52)	0.689	0.85
No	26 (52)	24 (48)		
Chronic kidney disease				
Yes	2 (4)	2 (4)	1.000	1.00
No	48 (96)	48 (96)		
Immunocompromised disease				
Yes	24 (48)	12 (24)	0.012	2.92
No	26 (52)	38 (76)		
ICU care				
Yes	15 (30)	10 (20)	0.248	1.71
No	35 (70)	40 (80)		
Hospitalization in the past one month				
Yes	26 (52)	21 (42)	0.316	1.49
No	24 (48)	29 (58)		

*OR = odds ratio

patients and ESBL-KP infection (p=0.004).[15] The increased risk for immunocompromised patients can be attributed to their chronic diseases, extensive use of therapies (particularly antibiotics), and frequent and prolonged hospitalizations.

Interestingly, this study did not find a correlation between the history of antibiotic use and ESBL-KP infection, contrary to a study conducted by Deng et al.[12] in China in 2017, which reported a 3.4 times higher risk of ESBL-KP infection associated with cephalosporin use.[12] Similarly, Demirdag and Hosoglu[9] found that antibiotic use for more than seven days was a risk factor for ESBL-KP (p=0.001).[9] It should be noted that in the Arifin Achmad Hospital, both case and control groups were exposed to antibiotics, but the study did not differentiate the exposure based on antibiotic class, duration, or administration method.

No correlation was found between diabetes mellitus and ESBL-KP infection, consistent with the study by Sharif et al.[10] in Iran (p=0.74).[10] However, Zhang et al.[11] found a correlation between diabetes mellitus and ESBL-KP, with diabetes mellitus patients having a 2.25 times higher risk of developing ESBL-KP compared to non-diabetic patients.[11] Many studies have indicated that diabetic patients have a higher risk of antibiotic resistance than non-diabetic patients.[16] Due to diabetic-associated complications and decreased immunity, diabetic patients are more susceptible to repeated bacterial infections and antibiotic exposure, particularly in countries with relatively less tight antibiotic use.[16] This study did not consider the duration and severity of diabetes mellitus.

Similarly, there was no correlation between

chronic kidney disease and ESBL-KP infection, consistent with studies by Sharif et al.[12] and Demirdag and Hosoglu[9] (p=0.8 and p=0.089). However, a study in Turkey found that patients with kidney disease had a 2.8 times higher risk of developing ESBL-KP compared to those without kidney disease.[9] Chronic kidney disease is a progressive decline in kidney function that may require dialysis or transplantation. Patients with chronic kidney disease have weakened immune systems and often experience prolonged and repeated hospital admissions, increasing their exposure to the hospital environment and cross-contamination. The degree of kidney damage was not considered in this study.

There was no observed association between ICU care and ESBL-KP infection in this study, which is consistent with a study conducted in Turkey (p=0.141).[9] However, Zhang et al.[11] found a correlation between ICU care and ESBL-KP infection.[11] ICU patients often require invasive devices such as urinary catheters and central venous catheters, and they also have longer hospital stays.[17] In this study, most ICU admissions were related to post-operative conditions, resulting in only a few days of ICU care.

Furthermore, this study did not find a correlation between a history of hospitalization in the past month and ESBL-KP infection. These findings differ from the research conducted by Demirdag and Hosoglu,[9] who found that a previous hospitalization history was a risk factor for developing ESBL-KP (p=0.031). The history of previous hospitalization was associated with a 1.58 times higher risk of developing ESBL-producing KP.[9] Zhang et al.[11] study also reported a correlation between hospitalization history and ESBL-KP (p=0.003).

This research indicates that immunocompromised conditions and hospitalization for more than 7 days are risk factors for infection by ESBL-producing *K. pneumoniae*. The presence of both of these risk factors in patients with infectious diseases should be considered when prescribing empirical antibiotics that cover such bacteria and implementing early contact precautions. The limitations of this study are: first, it is a prospective study, which means the data is only based on the medical record without confirmation from another source; second, the sample size is not large; and last, the patient source of infection is different from one patient to another.

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