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The Influence of Antibiotics Usage on Extended-spectrum β-lactamase-producing Enterobacter Colonization among Intensive Care Unit Patients

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Abstract

BACKGROUND: The prevalence of extended-spectrum beta-lactamases (ESBLs)-producing Enterobacteriaceae has increased throughout the world and is a major cause of treatment failure in intensive care unit (ICU). ESBL-producing Enterobacteriaceae exhibit resistance to cephalosporins which is one of the most commonly used and effective group of antibiotics.

AIM: The goal of this study was to identify the variables that influence the colonization of Enterobacteriaceae in patients treated at ICU.

PATIENTS AND METHODS: A prospective study involving randomized 70 patients was conducted at ICU of Sanglah General Hospital from October 2018 to March 2019. Specimens were obtained from rectal swabs on admission to and discharged from ICU. Initial bivariate analysis was conducted using Pearson's Chi-square and considered significant if $p < 0.05$. Adjusted relative risk ratio (RR) was used to estimate the influence of the variables to ESBL colonization.

RESULTS: Respiratory system dysfunction ($p = 0.012$, RR = 2.828) and antibiotic prescription before ICU admission ($p < 0.001$) influence ESBL-producing *Enterobacteriaceae* colonization on patient who was admitted to ICU. On discharged from ICU, ESBL colonization was associated to respiratory system dysfunction ($p = 0.008$, RR = 1.987), third-generation cephalosporin usage ($p = 0.009$, RR = 2.909), cefoperazone prescription ($p < 0.001$, RR = 8.471), ceftriaxone prescription ($p = 0.007$, RR = 6.316), and antibiotics usage duration ≥3 days ($p < 0.001$, RR = 7.071). The logistic regression results on influence of antibiotics usage and respiratory system dysfunction to ESBL colonization rate shows that both variables are independent risk factor to EBLS colonization both on admitted to and discharged from ICU.

CONCLUSION: The antibiotics usage and respiratory system dysfunction are independent risk factors to EBLS colonization in ICU patients.

Introduction

Extended-spectrum β-lactamases (ESBLs) are bacterial enzymes which are produced to confer resistance to broad range of extended-spectrum β-lactam antibiotics. The ESBLs hydrolyze extended-spectrum cephalosporins. First reports of ESBLs were in the mid-1980s and mostly *Klebsiella pneumoniae* and *Escherichia coli* [1]. In 2013, the Centers for Disease Control and Prevention reported an increasing resistance which included 26,000 ESBL-producing *Enterobacteriaceae* infections and 1700 deaths in the United States [2], [3].

Colonization of intensive care unit (ICU) patients with ESBL-producing *Enterobacteriaceae* on admission has an impact on poorer outcome and increasing mortality. A study in Egypt showed that 33% of the patients admitted to ICU were colonized with ESBL on one or more swab sites. The prevalence of ESBL-producing *Enterobacteriaceae* found in ICU patients rectal swabs varies throughout the world, 2.25% in the United States, 15% in France, 28.2% in South Korea, and 65% in India out of which 56% were ESBL-producing *E. coli* and 43% *Klebsiella* spp. [1], [4], [5].

Risk factors for infection with ESBL-producing organisms are prolonged antibiotic usage, prolonged treatment at ICU, recent invasive procedures, pressure ulcer, anemia, and permanent urinary catheter. Effective and rational usage of antibiotics in ICUs is important for the prevention of the development of antibiotic resistance [5], [6], [7]. The goal of this study was to identify the variables that influence the colonization of *Enterobacteriaceae* in patients treated at ICU. For the purpose of this study, *Enterobacteriaceae* are limited to *K. pneumoniae* and *E. coli*.

Patients and Methods

We conducted a prospective cohort study which was approved by the Ethical Committee of Sanglah General Hospital from October 1, 2018, until

March 31, 2019. Rectal swabs were collected from 70 randomized, adult patients who fulfilled the inclusion and exclusion criteria and willing to sign the informed consent when patients were admitted and discharged from ICU. Inclusion criteria included newly admitted ICU patients aged >18 years old who agreed to follow the study protocol after receiving consent to be included in this study. Exclusion criteria included those with known history of allergy to certain antibiotics and those who were treated at the ICU for <48 h.

Rectal swab specimens were put in transport medium and delivered to the Department of Clinical Microbiology of Sanglah General Hospital to be inoculated in MacConkey medium. After being incubated in 5% CO_2 for 18–24 h, the species were identified and susceptibility was tested using Vitek 2 Compact (BioMerieux, France).

We collected data regarding the study subject's previous antibiotics exposures (type and duration), coexisting conditions, invasive procedures, and other hospitalization-related and demographic information. Categorical variables were presented in percentage while numeric variables were presented in mean ± deviation standard (SD).

Initial bivariate analysis was conducted using χ^2 (Pearson's Chi-square) and considered significant if $p < 0.05$. Adjusted relative risk ratio (RR) was used to estimate the influence of the variables to ESBL colonization occurrence rate on the patient who was admitted or discharged from ICU. Statistical analysis was performed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

Table 1 shows the general characteristics of the patients. The mean age of the patients was 45.7 ± 17.75 years old, and 82.8% were adult (18–64 years old), with length of ICU stay for 6.35 ± 4.01 days. There were 57.1% of male patients with 61.4% of total patients were from Sanglah General Hospital inward patients. Most patients were exposed to ceftriaxone on admission to ICU. ESBL colonization increased during ICU stay from 25.7% at admission to 50% when patients were discharged from ICU (Table 2). The mortality rate was 22.9% (16 patients).

Our study shows that ICU stay causes an increase on ESBL-producing *Enterobacteriaceae* colonization rate from 25.7% (18 patients) at admission to 50% (35 patients) on ICU discharge with $p = 0.003$ ($p < 0.05$) and relative risk of 1.994, with a 95% confidence interval of 1.225–3.086 (Table 3). The study also finds that respiratory system dysfunction ($p = 0.012$, RR = 2.828) and antibiotic prescription before ICU admission ($p < 0.001$) influence ESBL-producing *Enterobacteriaceae* colonization on patient who was admitted to ICU (Table 4).

Table 1: General characteristic

Variable	n = 70
Age (years), mean ± SD	45.7 ± 17.75
18–64 years old, n (%)	58 (82.8)
≥65 years old, n (%)	12 (17.2)
Length of stay (days), mean ± SD	6.35 ± 4.01
Sex	
Male, n (%)	40 (57.1)
Female, n (%)	30 (42.9)
Previously treated at	
Other hospital, n (%)	27 (38.6)
Ward, n (%)	43 (61.4)

Table 2: Patient characteristic when admitted to and discharge from ICU

Variable	Time	
	Admitted to ICU	Discharge from ICU
Antibiotics		
Ceftriaxone, n (%)	42 (60)	38 (54.3)
Cefoperazone, n (%)	10 (14.3)	17 (24.3)
Cefazolin, n (%)	13 (18.6)	12 (17.1)
Non-cephalosporin, n (%)	5 (7.1)	3 (4.3)
Antibiotic usage duration		
<3 days, n (%)	51 (72.9)	21 (30)
≥3 days, n (%)	19 (27.1)	49 (70)
Mortality		
Yes, n (%)		16 (22.9)
No, n (%)		54 (77.1)
ESBLs colonization		
Positive, n (%)	18 (25.7)	35 (50)
Negative, n (%)	52 (74.3)	35 (50)

ESBLs: Extended-spectrum beta-lactamases, ICU: Intensive care unit.

On discharged from ICU (Table 5), we found that ESBL colonization was associated to respiratory system dysfunction ($p = 0.008$, RR = 1.987), third-generation cephalosporin usage ($p = 0.009$, RR = 2.909), cefoperazone prescription ($p < 0.001$, RR = 8.471), ceftriaxone prescription ($p = 0.007$, RR = 6.316), and antibiotics usage duration ≥3 days ($p < 0.001$, RR = 7.071).

Table 3: Comparative analysis of ESBLs colonization on admission and discharge from ICU

Variable	ESBL		p	RR 95% CI
	Positive	Negative		
ESBL				
Admission	35 (50)	35 (50)	0.003	1.994 (1.225–3.086)
Discharge	18 (25.7)	52 (74.3)		

ESBLs: Extended-spectrum beta-lactamases, ICU: Intensive care unit, RR: Risk ratio, CI: Confidence interval.

The logistic regression results on influence of antibiotics usage and respiratory system dysfunction to ESBL colonization rate shows that both variables are independent risk factor to EBLS colonization both on admitted to and discharged from ICU (Table 6).

Discussion

In this study, we identified and compared the ESBL-producing *Enterobacteriaceae* colonization on patients who were admitted and discharged from the ICU. Positive ESBL-producing *Enterobacteriaceae* colonization was found on 18 patients (25.7%) when

admitted to ICU. The number was increased to 35 patients (74.3%) on discharge. Thus, we found that antibiotics usage in critically ill patients was strongly associated to ESBL-producing *Enterobacteriaceae* colonization. The result was in line with a study by Harris *et al*. [8] which found 23 patients (23.7%) from a total of 97 patients became ESBL-producing *Enterobacteriaceae* carriers during ICUs stay. Young *et al*. [9] also observed similar results on his study in Singapore and concluded that ICUs stay was the risk factor of ESBL-producing *Enterobacteriaceae* colonization.

Table 4: Variables of ESBL colonization on ICU admission

Variable (n, %)	ESBL on admission		p value	RR (95% CI)
	Positive	Negative		
Sex				
Male	9 (22.5)	31 (77.5)	0.477	0.750
Female	9 (30)	21 (70)		(0.339–1.658)
Age				
Adult	14 (24.6)	43 (75.4)	0.644	0.798
Geriatric	4 (30.8)	9 (69.2)		(0.314–2.031)
Central nervous system dysfunction				
Present	10 (22.2)	35 (77.8)	0.370	0.694
Absent	8 (32)	17 (68)		(0.315–1.531)
Respiratory system dysfunction				
Present	12 (41.4)	17 (58.6)	0.012	2.828
Absent	6 (14.6)	35 (85.4)		(1.200–6.661)
Cardiovascular system dysfunction				
Present	9 (26.5)	25 (73.5)	0.888	1.059
Absent	9 (25)	27 (75)		(0.478–2.348)
Gastrointestinal system dysfunction				
Present	7 (38.9)	11 (61.1)	0.138	1.838
Absent	11 (21.2)	41 (78.8)		(0.841–4.016)
Urogenital system dysfunction				
Present	5 (31.3)	11 (68.7)	0.564	1.298
Absent	13 (24.1)	41 (75.9)		(0.545–3.091)
Musculoskeletal system dysfunction				
Present	3 (16.7)	15 (83.3)	0.578	0.308
Absent	15 (28.8)	37 (71.2)		(0.189–1.767)
Endocrine system dysfunction				
Present	5 (50)	5 (50)	0.058	2.308
Absent	13 (21.7)	47 (78.3)		(1.053–5.057)
Malignancy				
Present	5 (29.4)	12 (70.6)	0.689	1.199
Absent	13 (24.5)	40 (75.5)		(0.500–2.876)
Immune system dysfunction				
Present	0 (0)	5 (100)	0.172	1.383
Absent	18 (27.7)	47 (72.3)		(1.190–1.608)
Corticosteroid usage				
Present	4 (33.3)	8 (66.7)	0.507	1.381
Absent	14 (24.1)	44 (75.9)		(0.505–3.469)
Antibiotics				
Cephalosporin	16 (30.8)	36 (69.2)	0.100	2.769 (0.705–
Non–cephalosporin	2 (11.1)	16 (88.9)		10.885)
Antibiotics prescription before ICU admission				
Ceftriaxone	9 (21.4)	33 (78.6)	0.001	
Cefoperazone	7 (70)	3 (30)		
Cefazolin	0 (0)	13 (100)		
Others	2 (40)	3 (60)		
Antibiotics usage duration				
≥3 days	10 (37.0)	17 (63)	0.086	1.991
<3 days	8 (18.6)	35 (81.4)		(0.899–4.410)

ESBL: Extended-spectrum beta-lactamase, ICU: Intensive care unit, RR: Risk ratio, CI: Confidence interval.

Some statistically significant correlations could be observed in our study as the risk factor of ESBL-producing *Enterobacteriaceae* colonization in ICU patients. The previous studies throughout the world also demonstrated the increment of ESBL-producing *Enterobacteriaceae* colonization associated to cephalosporin usage [9], [10], [11]. A study in Croatia showed that ceftriaxone use was significantly correlated with ESBL occurrence ($p < 0.05$) and concluded that ceftriaxone derestriction increased the occurrence of ESBLs and the utilization of carbapemens [12].

Antibiotic usage with duration >3 days increases the risk of ESBL-producing *Enterobacteriaceae* colonization rate 7-fold higher ($p < 0.001$, RR = 7.071). Patients with respiratory system dysfunction are also at increasing risk to be carriers ($p = 0.008$, RR = 1.987). It may be associated to the third-generation cephalosporin usage such as cefoperazone and ceftriaxone as empirical antibiotic to treat pneumonia. An observational

Table 5: Variables of ESBL colonization on ICU discharge

Variable	ESBL colonization		p-value	RR 95% CI
	Positive	Negative		
Sex				
Male	22 (55)	18 (45)	0.334	1.269 (0.773–2.084)
Female	13 (43.3)	17 (56.7)		
Age				
Adult	28 (49.1)	29 (50.9)	0.759	0.912 (0.517–1.611)
Geriatric	7 (53.8)	6 (46.2)		
Central nervous system dysfunction				
Present	25 (53.1)	18 (41.9)	0.086	1.570 (0.903–2.730)
Absent	10 (37.0)	17 (63)		
Respiratory system dysfunction				
Present	25 (64.1)	14 (35.9)	0.008	1.987 (1.133–3.484)
Absent	10 (32.3)	21 (67.7)		
Cardiovascular system dysfunction				
Present	17 (54.8)	14 (45.2)	0.470	1.188 (0.746–1.893)
Absent	18 (46.2)	21 (53.8)		
Gastrointestinal system dysfunction				
Present	10 (52.6)	9 (47.4)	0.788	1.074 (0.645–1.788)
Absent	25 (49.0)	26 (51)		
Urogenital system dysfunction				
Present	9 (52.9)	8 (47.1)	0.780	1.079 (0.638–1.825)
Absent	26 (49.0)	27 (51)		
Musculoskeletal system dysfunction				
Present	9 (69.2)	4 (30.8)	0.124	1.518 (0.958–2.404)
Absent	26 (89.7)	3 (10.3)		
Endocrine system dysfunction				
Present	5 (45.5)	6 (54.5)	0.743	0.894 (0.757–1.958)
Absent	30 (50.8)	29 (49.2)		
Malignancy				
Present	12 (57.1)	9 (42.9)	0.434	1.217 (0.757–1.958)
Absent	23 (46.9)	26 (53.1)		
Immune system dysfunction				
Present	2 (66.7)	1 (33.3)	0.555	1.354 (0.587–3.124)
Absent	33 (49.3)	34 (50.7)		
Corticosteroid usage				
Present	7 (70)	3 (30)	0.172	1.500 (0.921–2.433)
Absent	28 (46.7)	32 (53.3)		
Central venous catheter usage				
Present	20 (58.8)	14 (41.2)	0.151	1.412 (0.880–2.280)
Absent	15 (41.7)	21 (58.3)		
Endotracheal tube usage				
Present	29 (49.2)	30 (50.8)	0.743	0.901 (0.495–1.640)
Absent	6 (54.5)	5 (45.6)		
Peripheral intravenous line				
Present	31 (47.7)	34 (52.7)	0.164	0.596 (0.359–0.990)
Absent	4 (80)	1 (20)		
Nasogastric tube				
Present	32 (53.3)	28 (46.7)	0.172	1.778 (0.670–4.717)
Absent	3 (30)	7 (70)		
Hemodialysis				
Present	4 (66.7)	2 (33.3)	0.393	1.376 (0.741–2.558)
Absent	31 (48.4)	33 (51.6)		
Mechanical ventilator				
Present	12 (63.2)	7 (36.8)	0.179	1.400 (0.886–2.214)
Absent	23 (45.1)	28 (54.9)		
Third-generation cephalosporin usage				
Yes	32 (58.2)	23 (41.8)	0.009	2.909 (1.032–8.203)
No	3 (20)	12 (80)		
Antibiotics usage in ICU				
Ceftriaxone	20 (52.8)	18 (47.4)	0.007	6.316 (0.944–42.252)
Cefoperazone	12 (70.6)	5 (29.4)	<0.001	8.471 (1.265–56.715)
Cefazolin	1 (8.3)	11 (91.7)	-	-
Others	2 (66.7)	1 (33.3)	0.024	8.000 (1.040–61.525)
Antibiotics usage duration				
≥3 days	33 (67.3)	16 (32.7)	<0.001	7.071 (1.865–26.807)
<3 days	2 (9.5)	19 (90.5)		

ESBL: Extended-spectrum beta-lactamase, ICU: Intensive care unit, RR: Risk ratio, CI: Confidence interval.

Table 6: Results of logistic regression on influence of antibiotics usage and respiratory system dysfunction to ESBL colonization rate

ESBL colonization	Variables tested	p-value	RR 95% CI
ESBL on admission	Antibiotics usage	0.062	4.895 (0.926–25.885)
	Respiratory system dysfunction	0.008	5.056 (1.529–16.712)
ESBL on discharge	Antibiotics usage	0.018	5.606 (1.342–23.425)
	Respiratory system dysfunction	0.013	3.773 (1.322–10.769)

ESBL: Extended-spectrum beta-lactamase, RR: Risk ratio, CI: Confidence interval.

multicenter study in France showed similar result with a significant correlation between ESBL-producing *Enterobacteriaceae* colonization and respiratory system dysfunction ($p < 0.01$), urogenital system dysfunction ($p < 0.01$), endocrine system dysfunction ($p < 0.01$), and immune system dysfunction ($p < 0.01$). Our study, however, reported significant correlation only on patients with respiratory system dysfunction [13].

In our study, invasive procedure variable analysis shows no significant correlation to ESBL-producing *Enterobacteriaceae* colonization with central venous catheter usage ($p = 0.151$), endotracheal intubation ($p = 0.743$), peripheral IV line ($p = 0.164$), nasogastric tube placement ($p = 0.172$), hemodialysis ($p = 0.393$), and mechanical ventilator ($p = 0.179$). The previous literatures showed various results in correlation with invasive procedure. Kawano *et al*. [14] and Repesse *et al*. [15] showed that mechanical ventilator ($p = 0.476$ and $p = 0.1$, respectively) had no statistically significant correlation to ESBL-producing *Enterobacteriaceae* colonization incidence. Another study, however, showed a different result that invasive procedure had strong correlation to ESBL-producing *Enterobacteriaceae* colonization with central venous catheters ($p < 0.01$), hemodialysis ($p < 0.01$), and mechanical ventilator ($p < 0.01$). The different result may be caused by the brief utilization of the invasive tools [13], [14], [15]. Further studies with larger sample size would help demonstrate the relationship of invasive procedure and ESBL-producing *Enterobacteriaceae* colonization.

Some limitations in our study included the fact that we collected no environmental sample that could cause ESBL-producing *Enterobacteriaceae* colonization by direct contact. The study was carried out only in ICU patients and no subsequent observations of morbidity and mortality were done after the patients were discharged from ICU.

Conclusion

The antibiotics usage and respiratory system dysfunction are independent risk factors to EBLS colonization in ICU patients.

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