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.

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 ESBL colonization both on admitted to and discharged from ICU.

CONCLUSION: The antibiotics usage and respiratory system dysfunction are independent risk factors to ESBL 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% CO₂ 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 χ² (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 aged ≥65 years old, 18–64 years old, and 82.8% were adult (18–64 years old). There were 57.1% of male patients with 61.4% of total.

| 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 (36.6) |
|                         | Ward, n (%)    |
|                         | 43 (61.4)      |

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 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)         |                    |
| 23 days, n (%)            | 19 (27.1)  | 49 (70)         |                    |
| Mortality                 |            |                 |                    |
| Yes, n (%)                | 16 (22.9)  | 54 (77.1)       |                    |
| No, n (%)                 | 52 (74.3)  | 35 (50)         |                    |
| 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                  | p             | RR 95% CI       |
|---------------------------|---------------|-----------------|
| ESBL                      |               |                 |
| Positive                  | 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 ESBLs 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) |
|----------------|-------------------|---------|-------------|
| Sex Male       | 9 (22.5)          | 0.477   | 0.750       |
| Sex Female     | 13 (30.1)         | 0.316   | 0.394–1.658 |
| Age Adult      | 14 (24.6)         | 0.644   | 0.788       |
| Age Geriatric  | 4 (30.8)          | 0.314   | 0.203–2.031 |
| Central nervous system dysfunction Present | 10 (22.2) | 0.370 | 0.694 |
| Central nervous system dysfunction Absent | 8 (32) | 0.315 | 1.321 |
| Respiratory system dysfunction Present | 12 (41.4) | 0.012 | 2.828 |
| Respiratory system dysfunction Absent | 6 (14.6) | 1.020 | 6.661 |
| Cardiovascular system dysfunction Present | 9 (26.5) | 0.888 | 1.059 |
| Cardiovascular system dysfunction Absent | 9 (25) | 0.478 | 2.348 |
| Gastrointestinal system dysfunction Present | 7 (38.9) | 0.138 | 1.838 |
| Gastrointestinal system dysfunction Absent | 11 (21.2) | 0.941 | 4.016 |
| Urogenital system dysfunction Present | 5 (31.3) | 0.564 | 1.258 |
| Urogenital system dysfunction Absent | 13 (45) | 0.545 | 3.091 |
| Musculoskeletal system dysfunction Present | 3 (16.7) | 0.578 | 0.308 |
| Musculoskeletal system dysfunction Absent | 15 (28.8) | 0.189 | 1.767 |
| Endocrine system dysfunction Present | 5 (50) | 0.058 | 2.308 |
| Endocrine system dysfunction Absent | 13 (21.7) | 1.003 | 5.057 |
| Malignancy Present | 5 (29.4) | 0.689 | 1.199 |
| Malignancy Absent | 13 (43.5) | 0.500 | 2.876 |
| Immune system dysfunction Present | 0 (0) | 1.172 | 1.383 |
| Immune system dysfunction Absent | 18 (27.7) | 1.190 | 1.608 |
| Corticosteroid usage Present | 4 (33.3) | 0.507 | 1.381 |
| Corticosteroid usage Absent | 14 (24.1) | 0.505 | 3.469 |
| Antibiotics Cefazolin | 16 (30.8) | 0.100 | 2.769 |
| Antibiotics Cefazolin Non-cefazolin | 2 (11.1) | 0.899 | 10.885 |
| Antibiotics prescription before ICU admission Ceftaxzone | 9 (21.4) | 0.000 | 0.001 |
| Antibiotics prescription before ICU admission Cefopen Azone | 7 (17.8) | 0.024 | 0.000 |
| Antibiotics prescription before ICU admission Cefazolin | 0 (0) | 0.819 | 1.991 |
| Antibiotics prescription before ICU admission Others | 2 (60) | 0.819 | 1.991 |
| Antibiotics usage duration ≥3 days | 10 (37.0) | 0.086 | 1.991 |
| Antibiotics usage duration <3 days | 8 (18.6) | 0.899 | 4.410 |

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 cefazolin usage [9], [10], [11]. A study in Croatia showed that ceftriaxone usage was significantly correlated with ESBL occurrence (p < 0.05) and concluded that ceftriaxone derescretion increased the occurrence of ESBLs and the utilization of carbapenems [12].

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

| Variable | ESBL colonization | p-value | RR 95% CI |
|----------|------------------|---------|-----------|
| Sex Male | 22 (55)          | 0.334   | 1.269     |
| Sex Female | 13 (33.3)       | 0.917   | 0.517     |
| Age Adult | 28 (49.1)        | 0.759   | 0.912     |
| Age Geriatric | 7 (53.8)     | 0.517   | 1.611     |
| Central nervous system dysfunction Present | 25 (53.1) | 0.886 | 1.570 |
| Central nervous system dysfunction Absent | 10 (27.0) | 0.903 | 2.730 |
| Respiratory system dysfunction Present | 25 (64.1) | 0.008 | 1.987 |
| Respiratory system dysfunction Absent | 10 (32.3) | 1.133 | 4.848 |
| Cardiovascular system dysfunction Present | 17 (54.8) | 0.470 | 1.786 |
| Cardiovascular system dysfunction Absent | 18 (46.2) | 1.158 | 0.893 |
| Gastrointestinal system dysfunction Present | 10 (25.6) | 0.788 | 1.074 |
| Gastrointestinal system dysfunction Absent | 25 (49.0) | 0.789 | 1.638 |
| Urinary system dysfunction Present | 9 (25.2) | 0.124 | 1.518 |
| Urinary system dysfunction Absent | 26 (49.0) | 0.958 | 2.404 |
| Musculoskeletal system dysfunction Present | 9 (69.2) | 0.124 | 1.518 |
| Musculoskeletal system dysfunction Absent | 26 (89.7) | 1.988 | 2.404 |
| Antibiotics usage Cefazolin | 17 (63) | 0.013 | 3.773 |
| Antibiotics usage Cefazolin Non-cefazolin | 33 (49.3) | 0.018 | 3.773 |
| Antibiotics usage duration ≥3 days | 33 (67.3) | 0.018 | 3.773 |
| Antibiotics usage duration <3 days | 23 (46.1) | 0.018 | 3.773 |

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

Table 5: Variables of ESBL colonization on ICU discharge

| Variable          | ESBL colonization | p-value | RR 95% CI |
|-------------------|-------------------|---------|-----------|
| Sex Male          | 22 (55)           | 0.334   | 1.269     |
| Sex Female        | 13 (33.3)         | 0.917   | 0.517     |
| Age Adult         | 28 (49.1)         | 0.759   | 0.912     |
| Age Geriatric     | 7 (53.8)          | 0.517   | 1.611     |
| Respiratory system dysfunction Present | 25 (53.1) | 0.886 | 1.570 |
| Respiratory system dysfunction Absent | 10 (27.0) | 0.903 | 2.730 |
| Cardiovascular system dysfunction Present | 17 (54.8) | 0.470 | 1.786 |
| Cardiovascular system dysfunction Absent | 18 (46.2) | 1.158 | 0.893 |
| Gastrointestinal system dysfunction Present | 10 (25.6) | 0.788 | 1.074 |
| Gastrointestinal system dysfunction Absent | 25 (49.0) | 0.789 | 1.638 |
| Urinary system dysfunction Present | 9 (25.2) | 0.124 | 1.518 |
| Urinary system dysfunction Absent | 26 (49.0) | 0.958 | 2.404 |
| Musculoskeletal system dysfunction Present | 9 (69.2) | 0.124 | 1.518 |
| Musculoskeletal system dysfunction Absent | 26 (89.7) | 1.988 | 2.404 |
| Antibiotics usage Cefazolin | 17 (63) | 0.013 | 3.773 |
| Antibiotics usage Cefazolin Non-cefazolin | 33 (49.3) | 0.018 | 3.773 |

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

ESBL 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 study found 23 patients (23.7%) which found 23 patients (23.7%) from a total of 97 patients became ESBL-producing Enterobacteriaceae carriers during ICUs stay.
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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