

Antibiotic Susceptibility Pattern of Extended-Spectrum Beta-Lactamase-Producing *Klebsiella Pneumoniae* and *Escherichia Coli*

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ABSTRACT

Extended-Spectrum Beta-Lactamase (ESBL) producing bacteria is a type of resistance that leads to complex management of patients in intensive care due to their resistance to first, second, and third-generation Cephalosporin and monobactam antibiotics. The most ESBL-producing bacteria are found in the family *Enterobacteriaceae*, especially *Klebsiella pneumoniae* and *Escherichia coli*. The purpose of this research was to determine the sensitivity pattern of ESBL-producing bacteria in Intensive Care Units (ICUs) of Ulin Hospital, Banjarmasin, in the period of 2016-2018. This research was a descriptive study with a cross-sectional approach using data from the laboratory medical records of patients with positive ESBL in the ICUs of Ulin Hospital, Banjarmasin, between 2016 and 2018. The research sample was taken by the total sampling method. This research obtained 216 isolates of ESBL-producing bacteria consisting of 155 (71.8%) isolates of *Klebsiella pneumoniae* and 61 (28.2%) *Escherichia coli*. It was found that the Cephalosporin antibiotics (Cefazolin, Cefotaxime, Ceftriaxone, and Cefepime) and monobactam antibiotic (Aztreonam) had the lowest sensitivity. Aminoglycoside antibiotics (Amikacin), Carbapenem (Ertapenem and Meropenem), and Tetracycline (Tigecycline) were the most sensitive antibiotics. It was concluded that both *Klebsiella pneumoniae* and *Escherichia coli* were the most dominant ESBL-producing bacteria and showed good sensitivity to the Amikacin, Ertapenem, Meropenem, and Tigecycline.

Keywords: Extended-spectrum beta-lactamase, *Klebsiella pneumoniae*, *Escherichia coli*, antibiotics susceptibility pattern, intensive care units

INTRODUCTION

Nosocomial infections, also known as Hospital-Acquired Infections (HAIs), are infections, which patients acquire since the first 48 hours of hospitalization. Infection can occur when the patient is being hospitalized or within 30 days of the hospital discharge.¹

The Intensive Care Unit (ICU) is a unit in the hospital specialized for patients with a high risk of HAIs. Both the ICU and Neonatal Intensive Care Unit (NICU) are part of the intensive care unit with staff and special equipment to support the observation and treatment of the patient whose potentially life-threatening conditions with an uncertain prognosis. Several factors such as a patient's low immune system, invasive monitoring of the patient's condition, exposure to various types of antibiotics, excessive use of antibiotics, and colonization by resistant bacteria can lead patients treated in ICU to a more tremendous potential for infection.²

Gram-negative bacteria, especially the *Enterobacteriaceae* family, become the most common cause of HAIs. Irrational use of antibiotics can cause mutations of Multidrug-Resistant Bacteria (MDR). Patients with MDR bacterial infections require more complex treatment than those with common bacterial infections because of the fewer drug choices and the higher dosage that can be used as a treatment for the patient's disease. Bacteria mostly cause Multidrug-resistant bacteria with the ability to produce enzymes that can hydrolyze beta-lactam antibiotics. This enzyme can hydrolyze Penicillin, first, second, and third generation of Cephalosporin and Monobactam antibiotics, and can be inhibited by Clavulanic acid and Carbapenem. Therefore, it is known as ESBL due to its broader resistance compared to other beta-lactamases-producing bacterial strains. Its resistance to various types of beta-lactam antibiotics makes the antibiotics not effective as a treatment. Extended-spectrum beta-lactamase is commonly

produced by Gram-negative bacteria, especially by the *Enterobacteriaceae* family, which is a cause of infection in the ICU and NICU in developing countries.³⁻⁷

Klebsiella pneumoniae and *Escherichia coli* are the most common ESBL-producing bacteria. Research on bacterial patterns in the ICU of Dr. Wahidin Sudirohusodo Hospital, Makassar, found that *Klebsiella pneumoniae* was the most prevalent bacteria (28.3%). Study in the ICU of Cipto Mangunkusumo Hospital in Jakarta, which aimed to determine the phenotypic characteristics of the *Enterobacteriaceae* family of Gram-negative bacteria, showed that *Klebsiella pneumoniae* was the most isolated bacteria (61 out of 112 isolates).²

As a major teaching hospital and the only tertiary hospital in South Kalimantan, ICU and NICU of Ulin General Hospital, Banjarmasin are always crowded with patients from various cities year-round, making both units an ideal location for bacterial growth and infections not only for patients but also visitors and workers in the units. In addition to the emergence of ESBL-producing bacteria, the everyday use of antibiotics without any prescription in the community raises concerns about antibiotic resistance and treatment failure. This fact had led authors to perform research that aimed to determine the sensitivity patterns of ESBL-producing bacteria in the ICU at Ulin General Hospital, Banjarmasin.

METHODS

This research was a retrospective descriptive study by taking data from patients' medical records with positive ESBL results of specimen culture in the ICU of Ulin General Hospital, Banjarmasin, in 2016-2018.

The population in this study was all patients treated in the ICU and NICU of Ulin General Hospital, Banjarmasin in 2016-2018, including medical records of all patients specimen culture and antibiotic sensitivity testing at the Clinical Pathology Laboratory of Ulin General Hospital, Banjarmasin. The research sample was taken from the medical record data of the Clinical Pathology Laboratory of Ulin Hospital, Banjarmasin, by the total sampling method.

The research instrument used in this study was the medical record, the results of specimen culture (blood, urine, pus, sputum, and other body fluids), and antibiotic sensitivity testing of all patients treated in the ICU at the Ulin General Hospital, Banjarmasin from 2016 to 2018. The data were

tabulated using Microsoft Excel 2010 and presented using frequency distribution table and percentage as the result of the study. The Ethical Committee of the Medical Faculty of Lambung Mangkurat University and Ulin General Hospital, Banjarmasin, approved the study protocol No. 444/KEPK-FK UNLAM/EC/IX/2019 and No. 210/VIII-Reg Riset/RSUDU/19, respectively.

RESULTS AND DISCUSSIONS

The results of this study performed in October-November 2019 found that of 9.333 culture requests in the Clinical Pathology Laboratory of Ulin Hospital, Banjarmasin from 2016 to 2018, 3.763 (40.3%) isolates showed positive bacterial results. Positive culture results of patients in the ICU were 1.178 isolates, which consisted of 745 (63.2%) positive isolates from the ICU and 433 (36.8%) positive isolates from the NICU. The study also found that positive culture results of *Klebsiella pneumoniae* and *Escherichia coli* bacteria in ICU were 301 isolates. Thus, a total of 207 (68.8%) and 94 isolates (31.2%) were identified as *Klebsiella pneumoniae* and *Escherichia coli*.

Table 1 shows a higher percentage of ESBL-producing than non-ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli*. The result of this research was consistent with research by Anong *et al.* at the Buddhachinaraj Hospital in Phitnasulok, Thailand, showing that 134 (62.3%) of 250 isolates were ESBL (+). The high number of ESBL-producing bacteria might be caused by several factors, such as exposure to various types of antibiotics and excessive use of antibiotics that trigger bacterial mutations into new strains of bacteria. The low immune system of patients in the ICU and NICU also results in susceptibility to infection.⁸

The results showed that most ESBL-producing (+) bacteria were *Klebsiella pneumoniae*. A study by n Taslim *et al.* in the ICU of Cipto Mangunkusumo Hospital also showed that *Klebsiella pneumoniae* was the most ESBL-producing bacteria as many as 61 (54.46%) of 112 isolates. This study was different from research by Bindu *et al.* in several hospitals in India that found *Escherichia coli* as the dominant bacteria, as many as 346 (41.4%) of 582 isolates. The number was less compared to the literature suggesting that Gram-negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli* are the most bacteria, which mutate into ESBL-producing bacteria.^{2,9}

Nagarajan *et al.*, in their research conducted at the Department of Microbiology, Allagapa University, mentioned that differences in the number of dominant bacteria could be due to differences in geography, hospital conditions, and different patient conditions. A closer similarity of conditions will lead to a more relative similarity of the bacterial pattern. Differences in the types of dominant microorganisms can also affect therapy or antibiotics as the primary therapeutic line. Irrational use of antibiotics can be one of the factors that cause the emergence of resistant bacteria. Proper administration of antibiotics should be begun with empirical antibiotics for patients who have bacterial infections without knowing the type of bacteria that infects them. Empirical antibiotics can be given for 48-72 hours while waiting for the results of laboratory tests. Administration of empirical therapy can be replaced by definitive treatment following the infecting bacterial strain.¹⁰

The study results showed that the positive culture results of the ESBL-producing *Klebsiella pneumoniae* were mostly derived from sputum specimens of

patients in the ICU (Table 2). The results of this study were consistent with research by Sinanjung *et al.* in the ICU of Dr. Soeradji Tirtonegoro Hospital at Klaten in 2019. The research found that the most ESBL-producing *Klebsiella pneumoniae* originate from sputum specimens in 36 (40.45%) of the total 89 isolates. The presence of bacteria in the results of sputum specimen culture can indicate an infection in the airways.¹¹

Taslim *et al.*, in their study, mentioned that one of the respiratory tract diseases with the highest incidence in the ICU is Ventilator-Associated Pneumonia (VAP). This disease is the most common type of nosocomial infection in ICU patients assisted with mechanical ventilation, using either endotracheal tubes or tracheostomy tubes. *Klebsiella pneumoniae* is a normal flora of the trachea and is a significant cause of pneumonia. The bacterial colonization of *Klebsiella pneumoniae* can cause the infection due to decreased immune system of patients treated in the ICU. Research by Luyt *et al.* in one of the hospitals in Paris in 2018 mentioned that risk factors for colonization of bacteria to cause VAP

Table 1. Distribution of *K.pneumoniae* and *E.coli* in ICUs of Ulin General Hospital in a period of 2016-2018

| Isolates | ICU | | NICU | |
|--|-----|------|------|------|
| | N | % | n | % |
| ESBL-producing <i>K.pneumoniae</i> | 106 | 73.6 | 49 | 77.7 |
| ESBL-non-producing <i>K.pneumoniae</i> | 38 | 26.4 | 14 | 22.2 |
| Total | 144 | 100 | 63 | 100 |
| ESBL-producing <i>E.coli</i> | 56 | 67.5 | 5 | 45.5 |
| ESBL-non-producing <i>E. coli</i> | 27 | 32.5 | 6 | 54.5 |
| Total | 83 | 100 | 11 | 100 |

Table 2. Distribution of *Klebsiella pneumoniae* ESBL-producing bacteria according to specimen culture in the ICUs of Ulin General Hospital 2016-2018

| Bacteria | Specimen | Room | | n | % |
|------------------------------|-------------------|------|------|-----|------|
| | | ICU | NICU | | |
| <i>Klebsiella pneumoniae</i> | Blood | 9 | 47 | 56 | 36.2 |
| | Urine | 6 | 0 | 6 | 3.9 |
| | Sputum | 76 | 0 | 76 | 49.0 |
| | Pus | 11 | 2 | 13 | 8.3 |
| | Other body fluids | 4 | 0 | 4 | 2.6 |
| | Total | 106 | 49 | 155 | 100 |
| <i>Escherichia coli</i> | Blood | 18 | 5 | 23 | 37.7 |
| | Urine | 8 | 0 | 8 | 13.1 |
| | Sputum | 9 | 0 | 9 | 14.8 |
| | Pus | 13 | 0 | 13 | 21.3 |
| | Other body fluids | 7 | 1 | 8 | 13.1 |
| | Total | 55 | 6 | 61 | 100 |

is the length of use of ventilators and the low immune state of patients. A study by Sansom on ICU patients using a ventilator at a Thai Hospital also showed the same type of bacteria in the oropharynx and the bacteria that cause VAP. This research showed that bacterial colonization in the oropharyngeal due to poor oral hygiene of the patients could also extend to the airways and cause VAP.^{12,13}

The results showed that the most positive culture results of ESBL-producing *Escherichia coli* were from blood specimens of patients in the ICU and NICU rooms (Table 2). The results of this study indicated similarities to previous studies conducted by Tsai *et al.*, which showed that the most *Escherichia coli* ESBL-producing bacteria were found in the blood specimens of patients treated in the NICU room. Positive culture results of ESBL-producing bacteria in blood specimens in the NICU room can indicate the presence of Bloodstream Infection (BSI) caused by bacteria or commonly refer to as bacteremia.

Escherichia coli in newborns can be due to a urinary tract infection from the baby's mother during the birth process. Factors such as low immune system in infants, low birth weight, and antibiotic exposure, especially third-generation Cephalosporin to infants while being treated in the NICU room, can also cause bacteremia in infants treated in the NICU room.⁴

The number of positive ESBL-producing *Escherichia coli* culture results in the blood specimen culture of ICU room patients can also be related. Based on research conducted by the European Center for Disease Prevention and Control, 48.3% of

cases of bacteremia were associated with the use of catheters, 32.6% are due to secondary infections, and 19.1% were due to unknown causes. Secondary infections developed from primary infection sites in the lungs (47.5%), gastrointestinal (17.2%), urinary tract (18.6%), surgical wounds (2.7%), skin and soft tissue (5.2%), and other body parts (5.2%).¹⁴

The results showed that *Klebsiella pneumoniae* and *Escherichia coli* had the lowest sensitivity to Cephalosporin (Cefazolin, Cefepime, Cefazolin, Ceftazidime, and Ceftriaxone) and Monobactam (Aztreonam) antibiotics from year to year (Figure 1-4). This result was consistent with the theory suggesting that ESBL-producing bacteria are resistant to beta-lactam antibiotics, especially Cephalosporin and Monobactam.¹⁵

Extended-spectrum beta-lactamase-producing bacteria resistance to antibiotics is caused by increased enzymatic activity in hydrolyzing beta-lactam antibiotics. Beta-lactamase enzymes produced by bacteria hydrolyze the beta-lactam ring possessed by most beta-lactam antibiotics, making antibiotics fail to bind to transpeptidase in bacterial walls. Resistance certainly has a significant influence in determining the therapy of the disease because Cephalosporin antibiotics are commonly used in hospitals. Resistance to Cephalosporin-class antibiotics results in the increasingly narrow choice of antibiotics that can be used in patients.^{6,16}

This study also found that Amikacin, Ertapenem, Meropenem, and Tigecycline had good sensitivity for bacterial infection caused by *Klebsiella pneumoniae* and *Escherichia coli* in ICU from 2016-2018. This finding was consistent with research conducted by

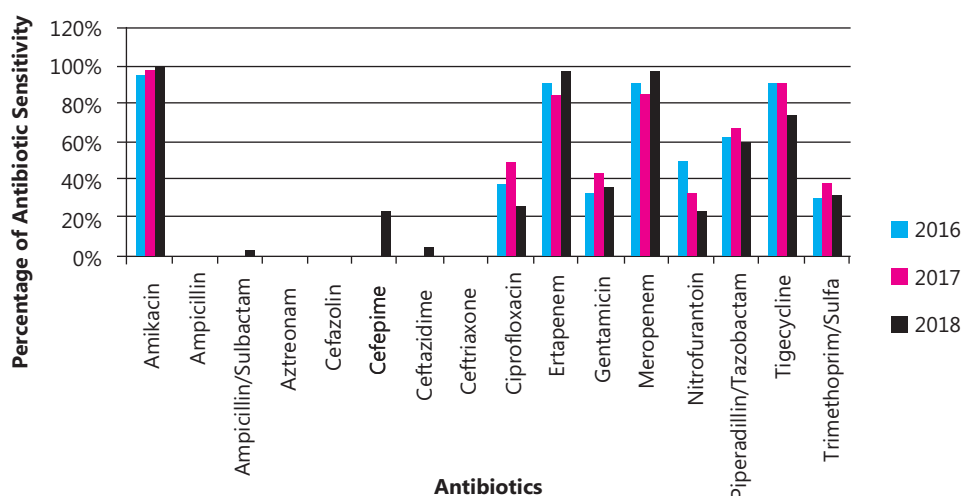


Figure 1. Sensitivity pattern of ESBL-producing *Klebsiella pneumoniae* in the ICU room at Ulin General Hospital in the period of 2016-2018

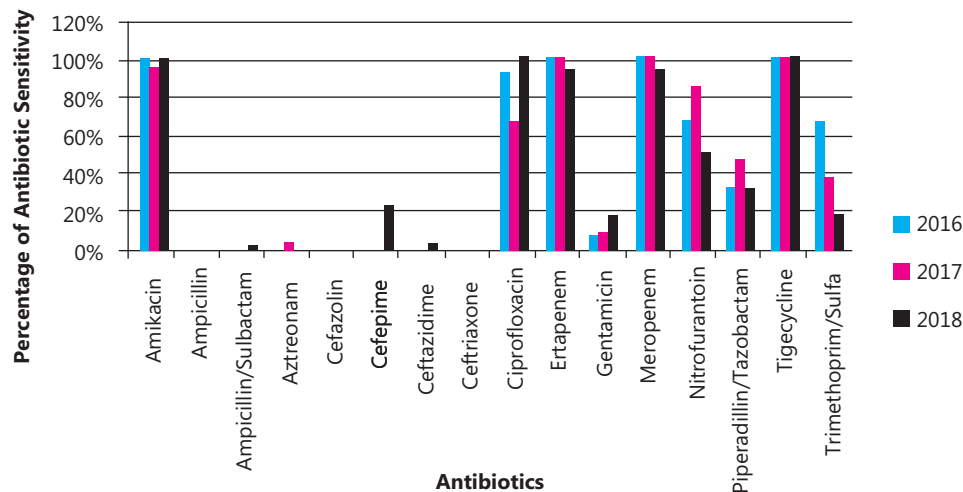


Figure 2. Sensitivity pattern of ESBL-producing *Klebsiella pneumoniae* in the NICU room at Ulin General Hospital, Banjarmasin in the period of 2016-2018

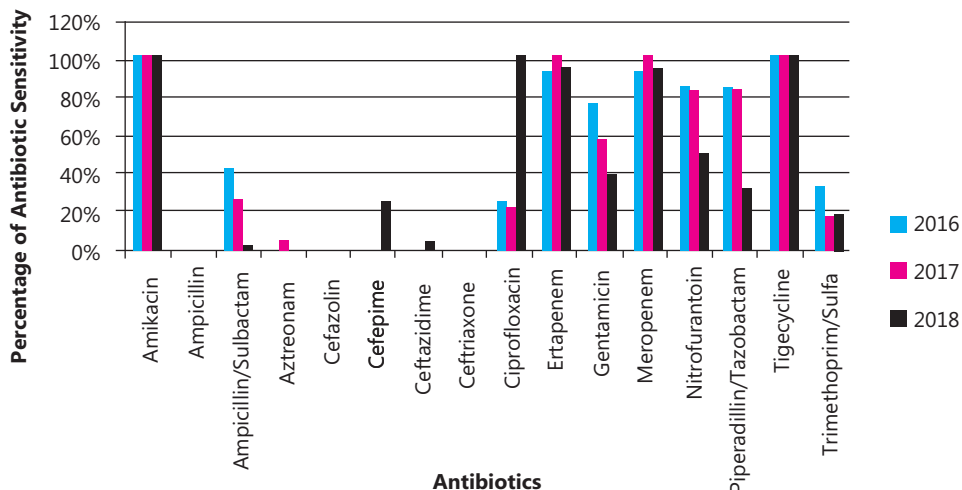


Figure 3. Sensitivity pattern of ESBL-producing *Escherichia coli* in the ICU room at Ulin General Hospital, in the period of 2016-2018

Sinanjung *et al.* in 2018 in the ICU room of Dr. Soeradji Tintonegoro General Hospital, which showed a >80% sensitivity on antibiotics such as Amikacin and Meropenem. The results of the study of *Klebsiella pneumoniae* bacteria in the NICU room and *Escherichia coli* bacteria in the ICU room showed an increased sensitivity in 2018.¹¹

The use of certain types of antibiotics that are rare in the case of infection in the ICU room is one factor influencing the enhanced antibiotic sensitivity. Cephalosporin-class antibiotics are often used as the first-line management of bacterial infection, cause resistance of bacteria due to continued exposure to the same antibiotics. Research conducted by Fauziyah

et al. at ICU Fatmawati Hospital in 2011 showed a significant relationship between the intensity of antibiotics given as a treatment with bacterial sensitivity. This study indicated that the continuous use of certain antibiotics in a certain period could increase bacterial resistance to these antibiotics.^{11,17}

Carbapenem-class antibiotics such as Ertapenem and Meropenem are not hydrolyzed by the beta-lactamase enzyme, enabling them to have good sensitivity to the ESBL-producing bacteria. This is because the Carbapenem antibiotic group has a slightly different beta-lactam ring from the Penicillin and Cephalosporin groups. Therefore, it is not easily hydrolyzed by the beta-lactamase enzyme.¹⁰

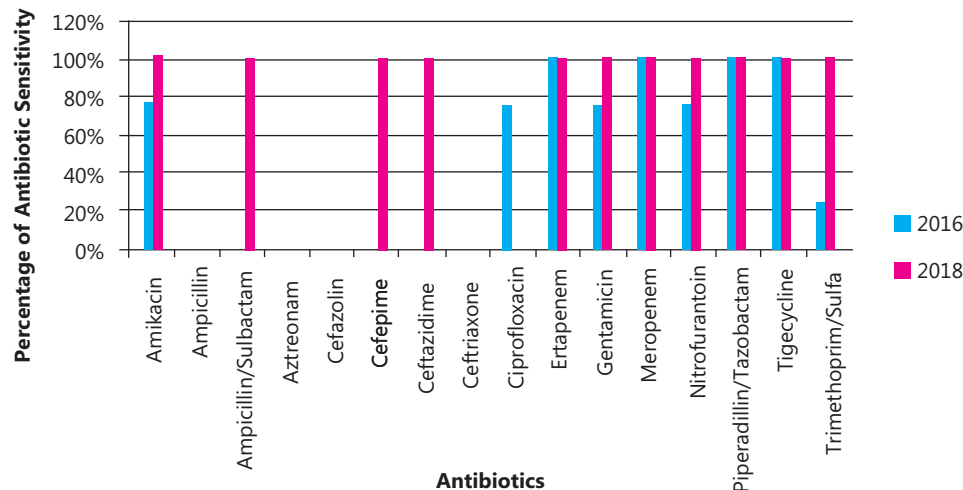


Figure 4. Sensitivity pattern of ESBL-producing *Escherichia coli* in the NICU room at Ulin General Hospital in the period of 2016-2018

CONCLUSIONS AND SUGGESTIONS

The study made several conclusions. First, the sensitivity pattern of the ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* in the ICU in 2016-2018 showed a consistent resistance to the Cephalosporin (Cefazolin, Ceftazidime, Ceftriaxone, and Cefepime) and Monobactam (Aztreonam). Second, antibiotics that were still effectively used in treating patients infected with ESBL-producing bacteria in the ICU of Ulin Hospital, Banjarmasin in 2016-2018 were Amikacin, Ertapenem, Meropenem, and Tigecycline because due to their excellent sensitivity.

The pattern of bacterial sensitivity to antibiotics is a dynamic phenomenon that similar studies need to be conducted every year. In future studies, it was recommended to include the results of clinical diagnosis from the patient's medical record to obtain bacterial sensitivity patterns based on the type of disease.

The results of this study can be used as a reference for rational selection of antibiotics in the treatment of patients treated in intensive care to reduce the risk of antibiotic resistance. Furthermore, reasonable antibiotic selection can also increase the effectiveness and efficiency of antibiotic use, especially in patients in the ICU of Ulin General Hospital, Banjarmasin.

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