# ESBL

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# Prevalence of Extended-Spectrum Beta Lactamase-Producing Microorganisms in Dr. Mohammad Hoesin Hospital Palembang

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## ABSTRACT

Production of Extended-Spectrum Beta-Lactamase (ESBL) by *Enterobacteriaceae* remains a problem for infectious diseases, especially in hospitals. The main causes of ESBL-producing bacteria colonization are urinary tract infections, length of hospital stay, invasive medical equipment, and antibiotics usage. This study aimed to compare the incidence of ESBL based on the type of organism in Dr. Mohammad Hoesin Hospital in 2017 and 2018. The research design used was descriptive with a cross-sectional approach which used secondary data at the Department of Clinical Pathology of Dr. Mohammad Hoesin Hospital, Palembang. The findings of this study showed a decreasing pattern in the incidence of ESBL in 2017 and 2018, but with a similar pattern, which was dominated by *Klebsiella pneumoniae* (followed by *Escherichia coli* and *Klebsiella ozaenae*) among inpatients in pediatric wards, internal medicine, and intensive care units, and on sputum specimens. This study showed the high prevalence of ESBL-producing bacteria (>60%) in Dr. Mohammad Hoesin Hospital, which was mainly caused by *Klebsiella pneumoniae*.

**Keywords:** Extended-spectrum beta lactamase, *Klebsiella pneumoniae*, *Enterobacteriaceae*

## INTRODUCTION

Infectious diseases are a major issue in developing countries such as Indonesia.[1] In addition to the high prevalence of disease, other issues such as irrational antibiotic use can lead to microbial resistance. Various surveillance data demonstrate a wide range of irrational antibiotic use, ranging from 12.5% (China), 37.8% (Pakistan) to 45.2% (Indonesia).[2-4]

Antibiotic resistance is a change in bacterial capacity to diminish the antibiotic action, mediated mostly by upregulation of drug efflux pumps.[5] Resistance initially began in hospitals, but it gradually spread across the community, particularly among *Streptococcus pneumoniae, Staphylococcus aureus,* and *Escherichia coli*.[6] Multi-resistant bacteria, including Methicilin-Resistant *Staphylococcus aureus* (MRSA) and Extended-Spectrum Beta Lactamase (ESBL)-producing bacteria dominated the incidence of resistance.[7] Infections caused by bacteria that generate ESBL have increased dramatically in recent years. The ESBL mediates the hydrolysis and inactivation of beta-lactam antibiotics, including third-generation Cephalosporins, Penicillins, and Aztreonam.[8]

Extended-spectrum beta lactamase is produced by mutations of beta-lactamase enzymes Temoneira-1 (TEM-1), Temoneira-2 (TEM-2), and Sulphydryl-1 (SHV-1), which are commonly found in the *Enterobacteriaceae* family. Penicillin and first-generation Cephalosporins are typically resistant to these enzymes.[9] The family *Enterobacteriaceae* has many genera such as *Escherichia coli, Klebsiella, Salmonella, Shigella, Enterobacter, Proteus*, and *Serratia* with about 20-25 species of clinical importance.[10] According to Nazmi *et al.* the prevalence of ESBL-producing *E.coli* and *K.pneumoniae* infections were 35% and 45%, respectively. In contrast to *K.pneumoniae*, ESBL production in *E.coli* was mostly found in outpatients.[11] The high occurrence of ESBL-producing bacteria serves as the landscape for this study, which compares the prevalence of ESBL based on the type of organism at the Dr. Mohammad Hoesin Hospital from 2017 to 2018.

## METHODS

This cross-sectional study used secondary data from the Department of Clinical Pathology and Microbiology of Dr. Mohammad Hoesin Palembang's Central General Hospital, a tertiary hospital in South Sumatra. Patients who underwent

culture and antibiotic resistance tests (outpatients and inpatients) between July-December 2017 and January-June 2018 were enrolled in this study. The inpatients originated from 15 wards, including the Emergency Room (ER), Intensive Care Unit/ICU (General, Pediatric, and Neonates), Internal Medicine (Komering), Neurology (Rawas and Brain and Health Center/BHC), Obstetrics and Gynecology (Enim), Oncology (Rambang), Ophthalmology (Kelingi), Otorhinolaryngology (Lematang), Pediatric (Kelingi), Respiratory (Borang), Surgery (Lakitan) and VIP (Musi). Patient data were collected using the total sampling technique, which included culture results and antibiotic resistance tests with ESBL bacteria. A double-disc approximation test (double disc synergy) was used as the screening test to identify ESBL strains.[12] The test was carried out by using the Cephalosporins antibiotics, including Cefotaxime (30 µg), Ceftazidime (30 µg), and Cefepime (30µg) placed 16-20 mm from the augmentin disc (20 µg of Amoxicillin and 10 µg of Clavulanic Acid). Positive results were interpreted based on the increase of Cephalosporins antibiotic inhibitory zone to the Clavulanic Acid disc.[13] The study was approved by the institutional review board of Universitas Sriwijaya, Faculty of Medicine, Palembang (approval number: 251/UN9.1.7/kepfkrsmh/2018).

A descriptive analysis of the variables collected was conducted; qualitative variables were expressed as percentages. The differences in the prevalence of ESBL producing-microorganism between 2017 and 2018 were analyzed using the Chi-Square or Fisher exact test, as appropriate. All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS®), version 26.0 (IBM SPSS Corp., Armonk, NY, USA) software.

## RESULTS AND DISCUSSIONS

The total ESBL-producing bacteria identified in this study showed decreasing pattern from 78.5% in 2017 to 60.3% in 2018. *Klebsiella pneumoniae* was the most commonly identified organism that produced the most ESBL during the study period (2017 and 2018), with 244 (49.4%) and 268 (56.0%) cases, respectively. Further bacterial findings followed a similar pattern in the consecutive years, with *Escherichia coli* and *Klebsiella ozaenae* as the second and third-highest organisms in terms of ESBL incidence (Table 1).

The incidence of ESBL caused by *Klebsiella pneumoniae*, *Escherichia coli*, and *Klebsiella ozaenae* bacteria was more frequently found in hospitalized cases between 2017 and 2018 (91.9% and 95.0%). Inpatient cases were dominated by *Klebsiella pneumoniae*, while outpatient cases were dominated by *Escherichia coli* (Figure 1).

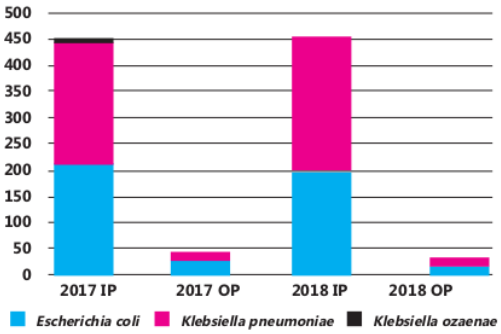


**Figure 1.** Prevalence of ESBL between outpatients and inpatients in 2017 and 2018

Note: Percentage was presented for the respective patients' group; IP=Inpatients, OP= Outpatients

**Table 1.** Prevalence of ESBL in 2017 and 2018

| Organisms | ESBL | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2017 | | | 2018 | | | p-value |
| | ESBL (+), % | ESBL (-), % | % of ESBL (+) | ESBL (+), % | ESBL (-), % | % of ESBL (+) | |
| *Escherichia coli* | 239, 83.3% | 48, 16.7% | 48.4 | 207, 54.0% | 177, 46.0% | 43.2 | <0.001[a] |
| *Klebsiella pneumoniae* | 244, 74.2% | 85, 25.8% | 49.4 | 268, 53.3% | 235, 46.7% | 56.0 | <0.001[a] |
| *Klebsiella ozaenae* | 11, 85.0% | 2, 15.0% | 2.2 | 4, 57.0% | 3, 43.0% | 0.8 | 0.290[b] |
| **TOTAL** | 494, 78.5% | 135, 21.5% | 100% | 479, 60.3% | 315, 39.7% | 100 | |

Note: a. Chi-Square test, b. Fisher's exact, level of significance was set at p<0.05

The general findings indicated that the internal medicine (Komering), pediatric (Selincah), and intensive care wards (IGD and GICU) were the most common places for ESBL findings, especially for the two dominant microorganisms in this study, *K.pneumoniae*, and *E.coli*. Figures 2-4 show the detailed type of ESBL bacteria based on treatment wards.

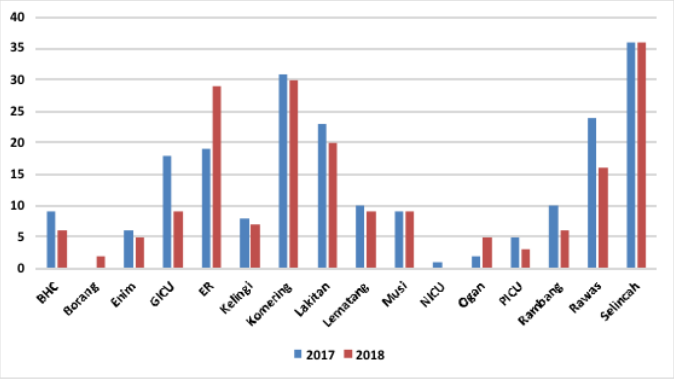


**Figure 2.** ESBL-producing *Escherichia coli* findings based on treatment wards

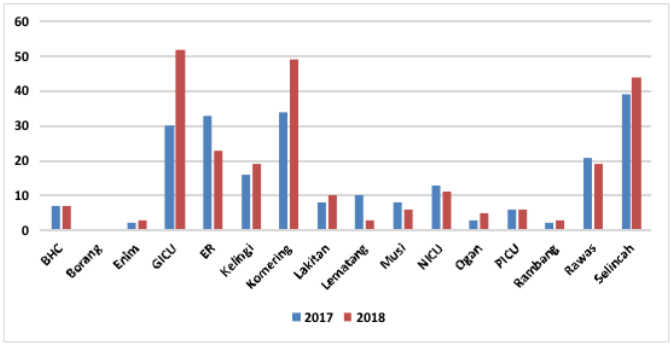


**Figure 3.** ESBL-producing *Klebsiella pneumoniae* findings based on treatment wards

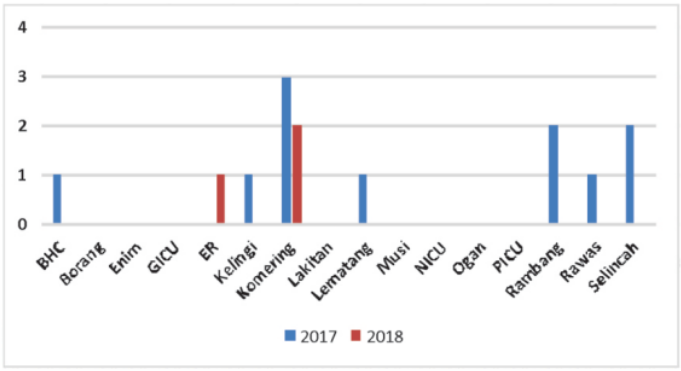


**Figure 4.** ESBL-producing *Klebsiella ozaenae* findings based on treatment wards

ESBL *E.coli* was mostly found in urine specimens in both periods (37.2% and 44.0%). Contrastingly, *K.pneumoniae* was frequently found in sputum (48.0% and 45.9%). However, *K.ozaenae* was mostly found in sputum samples in 2017 and urine samples in 2018. Table 2 presented the ESBL distribution based on specimens in 2017 and 2018.

In this study, the incidence of ESBL in Dr. Mohammad Hoesin Hospital decreased in 2018 compared to cases in 2017. Accurate data on the prevalence of ESBL-producing bacteria in Indonesia remain limited.[14] However, some studies found an increased incidence of ESBL in the *Enterobacteriaceae* family.[15-17] Nosocomial infections can play a role in this increase.[18] These infections can spread through direct or indirect contact and can originate in hospitals, clinics, or healthcare facilities.[19]

In various studies, an increased number of ESBL bacteria has been linked to an increase in antibiotic resistance cases.[20] This can have various consequences, including a reduction in the efficacy of antibiotics for exterminating bacteria (due to disruption of the target site, drug entry, and distribution inhibition), as well as a greater economic burden.[21] Inappropriate use of antibiotics in certain clinical situations, such as the administration of antibiotics in the absence of bacterial infection, improper antibiotic selection, and the use of excessive doses can cause transformation in bacterial strains to become more resistant.[22]

The most ESBL-producing bacteria found in this study were *K.pneumoniae, E.coli,* and *K.ozaenae* organisms, respectively. Data from Aceh, Indonesia revealed that *K.pneumoniae* was more common than *E.coli* in terms of ESBL infection (61% vs. 39%).[23] This was consistent with the literature, which states that bacteria from the *Enterobacteriaceae* family, particularly *K.pneumoniae* and *E.coli,* frequently produce the beta-lactamase enzyme.[24] *K.pneumoniae* usually infects immunodeficient persons, including alcoholics, diabetes mellitus, and chronic lung disease sufferers, leading to an increased risk of ESBL traits.[25] Meanwhile, ESBL-producing *E.coli* infection was associated with urinary catheterization due to urinary tract infections and irrational antibiotic use, particularly Penicillins and first-generation Cephalosporins.[26]

This study observed an overall decrease in ESBL-producing microorganisms between 2017 and 2018. It was presumed that the implementation of the Anti-Microbial Resistance Control Program (Program Pengendalian Resistensi Antimikroba/ PPRA) has taken a role in this phenomenon. After its implementation, a study has stated that the quality of antibiotics usage rises above 50% in terms of appropriate and rational use.[27] A study found the use of more proper prophylaxis antibiotics for surgery (first-generation Cephalosporins rather than third-generation Cephalosporins) after PPRA implementation.[28] Antimicrobial resistance can be reduced by proper use of antibiotics (including the type, dose, indication, interval, and route of administration).[27]

In this study, inpatients had a higher rate of ESBL than outpatients. These findings were consistent with those from Nigeria, which found that hospitalized patients were more likely to have positive ESBL traits (54.9% vs 20.2%).[29] A study in Turkey found that the highest prevalence was found in inpatients with ESBL-producing *K.pneumoniae* (25%-60.5%) and the lowest prevalence was found in outpatients with ESBL-producing *E.coli* (9.6%-22.8%).[15] Pediatric wards, internal medicine, and intensive care units were the most commonly

**Table 2.** Distribution of ESBL based on collected specimens

| Specimen Type | *E.coli* | | | | *K.pneumoniae* | | | | *K.ozaenae* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2017 | | 2018 | | 2017 | | 2018 | | 2017 | | 2018 | |
| | n | % | n | % | n | % | N | % | n | % | n | % |
| Sputum | 37 | 15.5 | 31 | 15.0 | 117 | 48.0 | 123 | 45.9 | 5 | 46.0 | 1 | 25.0 |
| Blood | 13 | 5.4 | 14 | 7.0 | 35 | 14.3 | 28 | 10.4 | 1 | 9.0 | 0 | 0 |
| Pus | 54 | 23.0 | 38 | 18.0 | 15 | 6.1 | 32 | 12.0 | 1 | 9.0 | 1 | 25.0 |
| Swab | 18 | 7.5 | 14 | 7.0 | 13 | 5.3 | 16 | 6.0 | 1 | 9.0 | 0 | 0 |
| Urine | 89 | 37.2 | 92 | 44.0 | 45 | 18.4 | 54 | 20.1 | 3 | 27.0 | 2 | 50.0 |
| **Other body** | | | | | | | | | | | | |
| Fluids | 13 | 5.4 | 8 | 4.0 | 12 | 5.0 | 9 | 3.4 | 0 | 0 | 0 | 0 |
| Feces | 15 | 6.0 | 10 | 5.0 | 7 | 2.9 | 6 | 2.2 | 0 | 0 | 0 | 0 |
| **Total** | 239 | 100 | 207 | 100 | 244 | 100 | 268 | 100 | 11 | 100 | 4 | 100 |

affected rooms of inpatients. The findings were similar to those from previous studies, which identified intensive care, pediatric wards, and internal medicine as the most common infection sites for ESBL-producing bacteria.[30] The high density of patients admitted to the internal medicine and pediatric wards facilitate the horizontal spread of resistant genes through conjugation, transduction, and transformation modes.[31] According to a systematic review, ESBL-producing bacteria were found more frequently in children than in adults, particularly in the intensive care unit, and were associated with immature immunity status in children.[32] High rates of antibiotic use and long length of stay in intensive care units also increase the risk of ESBL colonization and infection.[33] According to a study conducted in Makassar, 53.7% of the ICU isolates examined had multi-drug resistant organisms.[34]

Extended-spectrum beta lactamase-producing bacteria were found in a variety of specimens, depending on the type of bacteria (Table 2). Urine specimens were the most common source of *E.coli*, while sputum was the most frequent site of *K.pneumoniae*. In a previous study in Pekanbaru, the dominance of *K.pneumoniae* in sputum was also demonstrated (43.7%).[35] Previous research in Nepal, Bangladesh, and Indonesia revealed a prevalent *E.coli* profile in urine.[23,36,37] However, another study from Indonesia showed that the majority of *E.coli* was found in pus.[35]

## CONCLUSIONS AND SUGGESTIONS

The prevalence of ESBL-producing bacteria is relatively high at Dr. Mohammad Hoesin Hospital, with more than 60% of cases in 2017 and 2018. The most common ESBL-producing bacteria found in inpatients treated in the pediatric wards, internal medicine, and intensive care units were *Klebsiella pneumoniae*. The pattern of ESBL-producing bacteria varied depending on the specimen, with *K.pneumoniae* as the most common bacteria in sputum and *E.coli* as the most common bacteria in the urine. Additional research could be focused on determining the risk factors for infection with ESBL-producing *Enterobacteriaceae* in the affected population.

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