

## **PREVALENCE OF ESBL-PRODUCING AND CARBAPENEM RESISTANT ENTEROBACTERIACEAE AT DR. H. ABDUL MOELOEK GENERAL HOSPITAL, LAMPUNG, INDONESIA**

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**Abstract :** *Prevalence of ESBL-Producing and Carbapenem Resistant Enterobacteriaceae at Dr. H. Abdul Moeloek General Hospital, Lampung, Indonesia.* Enterobacteriaceae producing Extended-Spectrum Beta-Lactamase (ESBL) and resistant to carbapenem class antibiotics impact the high mortality rate and limitations in therapy.. This study aimed to assess the prevalence of ESBL-producing Enterobacteriaceae and Carbapenem resistant too in clinical isolates obtained from Dr. H. Abdul Moeloek General Hospital, Lampung. A total of 311 Enterobacteriaceae isolates were collected from various clinical specimens, including blood, urine, sputum and wound cultures, between January to December 2022. Identification and antimicrobial susceptibility testing were performed using standard microbiological techniques, with VITEK2 compact automated system. Carbapenem resistance and ESBL production were detected automatically. The results was found prevalence a 1,93% of Enterobacteriaceae ESBL-producing strains and carbapenem resistant, consisting of 50 % in *Escherichia coli*, 33,4 % in *Klebsiella pneumoniae* and 16,6% in *Burkholderia cepacia*. The study also found significant resistance patterns to other common antibiotics, highlighting the urgent need for improved surveillance and antimicrobial stewardship practices, continuous monitoring and the development of effective strategies to combat the growing threat of multidrug-resistant organisms in hospital.

**Keywords :** Prevalence, ESBL producing Enterobacteriaceae, Carbapenem resistant

**Abstrak :** *Prevalensi Bakteri Enterobacteriaceae penghasil-ESBL dengan Resisten Karbapenem di Rumah Sakit Umum Dr. H. Abdul Moeloek, Lampung, Indonesia.* Enterobacteriaceae penghasil Extended spectrum betalactamase (ESBL) dan resisten terhadap karbapenem berdampak pada tingginya angka kematian dan keterbatasan dalam melakukan terapi. Penelitian ini bertujuan untuk mengetahui prevalensi Enterobacteriaceae penghasil ESBL dan resisten karbapenem pada isolat klinis yang diperoleh dari Rumah Sakit Umum Dr. H. Abdul Moeloek, Lampung. Sebanyak 311 isolat bakteri kelompok Enterobacteriaceae dari berbagai spesimen klinis termasuk darah, urin, sputum, dan swab luka selama periode Januari hingga Desember 2022. Identifikasi dan uji sensitifitas antimikroba dilakukan menggunakan teknik mikrobiologi standar dengan alat sistem otomatis Vitek2 compact. Adanya resistensi karbapenem dan produksi ESBL dideteksi secara otomatis. Hasil penelitian mendapatkan prevalensi Enterobacteriaceae penghasil ESBL yang resisten terhadap karbapenem sebanyak 1,93%, terdiri dari 50% pada *Escherichia coli*, 33,4% pada *Klebsiella pneumoniae*, dan 16,6 % pada *Burkholderia cepacia*. Penelitian ini juga mendapatkan tingkat resistensi yang signifikan terhadap antibiotik, sehingga perlunya peningkatan pengawasan dan penatagunaan antimikroba, pemantauan terus-menerus dan pengembangan strategi efektif untuk

mengatasi ancaman peningkatan bakteri yang resisten terhadap berbagai antibiotik di Rumah Sakit.

**Kata Kunci** : Prevalensi, *Enterobacteriaceae* penghasil ESBL, Resisten Karbapenem

## INTRODUCTION

Antibiotic resistance is a growing global problem that threatens the effectiveness of infection therapies and increases the mortality rate associated with preventable infections. One of the main causes of antibiotic resistance is the production of Extended-Spectrum  $\beta$ -Lactamase (ESBL) in *Enterobacteriaceae* bacteria, as well as resistance to carbapenems, which are the last class of antibiotics still effective against infections caused by multidrug-resistant pathogens. (WHO, 2014).

*Enterobacteriaceae* have been classified as severely drug resistant bacteria by the World Health Organization due to their extensive production and dissemination of carbapenemases and extended-spectrum  $\beta$ -lactamases. ESBL-producing *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumoniae*, can break down various types of  $\beta$ -lactam rings, including third-generation cephalosporins, which are widely used in the treatment of nosocomial infections. Additionally, the development of carbapenem resistance in these bacteria is increasingly concerning, as there are few therapeutic alternatives available for infections caused by carbapenem-resistant bacteria. This phenomenon affects hospitals' ability to provide effective treatment and exacerbates patient burden and healthcare costs. (Nordmann, 2019).

Previous studies in various countries, including Indonesia, have reported a significant increase in the prevalence of ESBL-producing and carbapenem-resistant bacteria. According to a study conducted by Suyanto, 2012 and Tjahjadi, 2021 was found the prevalence of *Klebsiella pneumoniae* and *Escherichia coli* producing ESBL has shown a continuous rise in many hospitals in Indonesia. Additionally, several studies have indicated that uncontrolled antibiotic use and suboptimal infection management

have contributed to the spread of resistant bacteria (Suyanto et al., 2019; Tjahjadi et al., 2021).

In Indonesia, data on the prevalence of ESBL-producing *Enterobacteriaceae* and carbapenem-resistant bacteria in hospitals are still limited. Therefore, this study was conducted to determine the prevalence of ESBL-producing *Enterobacteriaceae* and carbapenem-resistant bacteria at Dr. H. Abdul Moeloek General Hospital, Lampung, Indonesia, from January to December 2022.

## MATERIALS AND METHODS

### Study Design and Sample :

This is a retrospective study was conducted in Microbiology Division, Clinical Pathology Laboratory at Dr. H. Abdul Moeloek General Hospital, Lampung Province. Inclusion criteria were *Enterobacteriaceae* isolates demonstrating resistance to one or more antibiotics in three or more different classes, based on susceptibility testing, consistent with the definition of multidrug-resistant organisms (MDRO). The results of a second repeat susceptibility test were considered as exclusion criteria. A total of 311 bacteria isolates for the period between January to December 2022 included in this study.

### Bacterial isolates :

Bacterial isolates were collected from different sources, including blood, sputum, urine, and wound swab from various rooms. The isolates were cultured on Nutrient agar plates and Mac conkey agar and incubated for 24 hours at 37° C. Bacterial identification was performed using the Vitek2 Compact system.

### Bacterial identification :

Bacterial identification was performed using the Vitek2 Compact system is based on automated biochemical analysis using specialized identification cards. A bacterial suspension of standardized turbidity is inoculated into the card, which contains various biochemical

substrates. The card is then incubated and automatically read by the instrument, detecting color or turbidity changes resulting from bacterial metabolic activity. The biochemical reaction data are compared with the system's internal database to rapidly and accurately determine the bacterial identity.

**Antimicrobial susceptibility testing :**

Antimicrobial susceptibility testing was performed using the Vitek2 Compact system with standardized inoculum. The VITEK system tests bacterial susceptibility using a panel of antibiotics. For Gram-negative bacteria, it includes penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, tetracyclines, and trimethoprim-sulfamethoxazole. The exact antibiotics tested depend on the specific VITEK AST card used. The testing was conducted according to the Clinical and Laboratory Standards Institute (CLSI) standards (24<sup>th</sup> edition).

**Identification of ESBL producing and Carbapenem resistant :**

The identification of ESBL producing bacteria and resistant of Carbapenem was performed automatically using Vitek2 compact system. ESBL detection is based on how the organism responds to certain  $\beta$ -lactam antibiotics alone and in

combination with a  $\beta$ -lactamase inhibitor (clavulanic acid). The VITEK 2 compares bacterial growth in the presence of the antibiotics alone versus with clavulanic acid; reduced growth in the presence of the antibiotic-clavulanate combinations indicates ESBL production.

**Statistical Analysis :**

Statistical analysis was performed descriptively by calculating the frequency distribution and presented in the form of a frequency table.

**Quality Control :**

This study, used the two American Type Culture Collection, USA (ATCC) strains *Klebsiella pneumoniae*. ATCC 13883 is the negative control and ATCC 700603 is the ESBL positive control.

**RESULTS AND DISCUSSION**

During the period from January to December 2022, the results of the resistance culture examination revealed that 311 bacterial isolates that grew were from the Enterobacteriaceae group, with the highest prevalence being *Klebsiella pneumoniae* (45,98%), followed by *Escherichia coli* (38,26%), as shown in Table 1. A total of 17 species from the Enterobacteriaceae group were successfully identified from various specimens such as blood, sputum, urine, and wound swabs.

**Table 1. Distribution of Enterobacteriaceae during the period from January to December 2022 (n=311)**

No.	The name of Bacteria	Number	%
1.	<i>Klebsiella pneumoniae</i>	143	45,98
2.	<i>Escherichia coli</i>	119	38,26
3.	<i>Sphingomonas paucimobilis</i>	14	4,50
4.	<i>Burkholderia cepacia</i>	8	2,57
5.	<i>Enterobacter aerogenes</i>	4	1,28
6.	<i>Raoultella ornithinolytica</i>	4	1,28
7.	<i>Enterobacter cloacae</i>	3	0,96
8.	<i>Proteus mirabilis</i>	3	0,96
9.	<i>Citrobacter freundii</i>	3	0,96
10.	<i>Serratia marcescens</i>	2	0,64
11.	<i>Alcaligenes faecalis</i>	1	0,32
12.	<i>Chryseobacterium indologenes</i>	1	0,32
13.	<i>Elizabethkingia meningoseptica</i>	1	0,32
14.	<i>Raoultella planticola</i>	1	0,32
15.	<i>Rhizobium radiobacter</i>	1	0,32
16.	<i>Serratia ficaria</i>	1	0,32
17.	<i>Serratia fonticola</i>	1	0,32

	Totally	311	100
<p>As shown in Table 1, <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i> remain the main ESBL-producing bacteria found in the hospital. Similar results were also obtained at Arifin Achmad Regional General Hospital, Pekanbaru, Riau, in a study by Anggraini D et al, with notably high proportions of 66.65% in <i>Klebsiella pneumoniae</i> and 66.25% in <i>Escherichia coli</i>. (Anggraini, et al. 2018). Another study by Zahrah CF, et al, at Dr. Mohammad Hoesin General Hospital, Palembang, also reported ESBL prevalence of 53.6% in <i>Klebsiella pneumoniae</i> and 72.1% in <i>Escherichia coli</i>.</p>			

The results of this study are similar to the findings of Mustafai et al., 2022, in Pakistan, 26.04% of the patients were from infections with *Enterobacteriaceae* which found *Escherichia coli* was the most prevalent (9.1%) isolate overall, followed by *Klebsiella pneumoniae* (8.07%). (Mustafai et al, 2022). *Klebsiella pneumoniae* and *Escherichia coli* are among the most prevalent *Enterobacteriaceae* species found in human infections due to several factors like the bacteria are naturally found in the human gastrointestinal tract, which makes them readily available to cause infections, particularly when they migrate to other body sites such as the urinary tract, bloodstream, or

respiratory system. These bacteria possess a variety of virulence factors, such as pili, adhesins, and siderophores, which allow them to adhere to host tissues, evade immune responses, and acquire essential nutrients. This increases their ability to colonize and infect human tissues. (Murray, C. J., et al. 2024).

Multi-drug-resistant (MDR) *Enterobacteriaceae* infections represent a serious concern to public health because of their high mortality rates. Major contributors to antimicrobial resistant include extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenemases produced by *Enterobacteriaceae*. (Sing SR, 2021). Carbapenems are broad-spectrum antibiotics considered highly effective in treating infections caused by multidrug-resistant bacteria. Carbapenem-resistant *Enterobacteriaceae* (CRE), including carbapenem-producing *E. coli* and *Klebsiella* isolates, have become a major concern as they limit treatment options. As shown in Table 2, the results of this study indicate that out of the 311 isolates identified, 1,93% all of them, the bacteria that produce ESBL and are also resistant to carbapenems. Those bacteria are *Escherichia coli* (50,0%), *Klebsiella pneumoniae* (33,4%) and *Burkholderia cepacia* (16,6%).

**Table 2. Distribution of ESBL-producing *Enterobacteriaceae* and Carbapenem-resistant (n=6)**

No.	Name of Bacteria	Number	%
1.	<i>Escherichia coli</i>	3	50,0
2.	<i>Klebsiella pneumoniae</i>	2	33,4
3.	<i>Burkholderia cepacia</i>	1	16,6
Totally		6	100

The result as the same from Arumugam K, 2024 was found that carbapenemase production was detected in 72 isolates (24%), consist in 46 (63.8%) were identified as *Klebsiella* and 26 (36.1%) as *E. coli*. (Arumugam k, 2024). A study conducted at Prof. Dr. Margono Soekarjo Purwokerto Regional General Hospital by Afifah et al found

that 5% of ESBL-producing *Klebsiella spp.* were resistant to meropenem. Another study by Anggraini D et al, at Arifin Achmad Regional General Hospital, Pekanbaru, reported a prevalence of meropenem-resistant ESBL-producing *Klebsiella pneumoniae* of 6% and 2% in *Escherichia coli*. The low prevalence observed indicates that both bacteria

remain highly sensitive to meropenem. This finding also suggests that the use of carbapenem-class antibiotics is still well controlled, as carbapenems are currently considered the drugs of choice for infections caused by ESBL-producing bacteria. Differences in prevalence rates may also be influenced by the limited detection of ESBL-producing bacterial groups, which could be related to the relatively low number of culture examinations performed.

Carbapenem-resistant *Enterobacteriaceae* (CRE) are among the most important antibiotic-resistant bacteria, making them highly dangerous. The multidrug resistance rates in *Escherichia coli* and *Klebsiella pneumoniae* are reported to be 30% and 50%, respectively, by the Indian Council of Medical Research. The other result from Ali, SA et al, 2024, provides insights into the rising prevalence of

*Klebsiella pneumoniae* and *E. coli* as carbapenem-resistant pathogens in hospital settings, particularly in Pakistan.

From Table 3, it can be seen that ESBL-producing and carbapenem-resistant bacteria can be found anywhere, although they are most likely to be found in intensive care units, considering that patients in intensive care are typically in a condition with multiple complications. The study found that 33.3% of these bacteria were found in the intensive care unit. Patients in ICUs are often critically ill, with weakened immune systems due to underlying conditions, surgery, or trauma. This makes them more vulnerable to infections, including those caused by *Klebsiella pneumoniae* and *Escherichia coli*, which can colonize and infect patients more easily. (Martínez, L., et al. 2024).

**Table 3. Distribution of rooms where ESBL-producing Enterobacteriaceae and Carbapenem-resistant bacteria were found (n=6)**

No.	Name of Bacteria	Room			
		ICU	Pulmo	VIP	Surgeon
<b>Isolation</b>					
1.	<i>Escherichia coli</i>	1	-	1	1
2.	<i>Klebsiella pneumoniae</i>	1	1	-	-
3.	<i>Burkholderia cepacia</i>	-	-	-	-
Totally		2	1	1	1

Intensive Care Units frequently involve invasive procedures such as catheterization, mechanical ventilation, and surgery. These procedures provide direct access to internal body sites, facilitating the entry of resistant pathogens like *Klebsiella* and *Escherichia coli* into the body. ICUs are high-risk environments for hospital-acquired infections (HAIs), where the transmission of resistant bacteria is more likely due to the close proximity of patients, healthcare workers, and medical equipment. (Liu, Y., et al. (2024).

Carbapenem Resistant *Enterobacteriaceae* bacteria cause

various infection syndromes, including bloodstream, respiratory tract, intra-abdominal, and urinary tract infections. These infections impose a significant global burden, with limited treatment options, primarily due to high antibiotic resistance rates (Murray CJ, 2022). From Table 4 shows that the three species found during this one-year period are bacteria that have become resistant to various types of antibiotics. This provides evidence that *Enterobacteriaceae* species that produce ESBL and are also resistant to carbapenems are multidrug-resistant and should be closely monitored.

**Table 4. Sensitivity patterns of ESBL-producing Enterobacteriaceae and Carbapenem-resistant bacteria against various antibiotics**

No.	Antibiotika <i>Burkholderia cepacia</i>	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	
		S (%)	S (%)	S (%)
1.	Ampicillin	0	0	0
2.	Ampicillin Sulbactam	0	0	0
3.	Piperacillin Tazobactam	0	0	0
4.	Cefazolin	0	0	0
5.	Ceftazidime	0	0	0
6.	Ceftriaxone	0	0	0
7.	Cefepime	0	0	0
8.	Aztreonam	0	0	0
9.	Ertapenem	0	0	0
10.	Meropenem	0	0	0
11.	Amikasin	0	0	0
12.	Gentamisin	0	0	0
13.	Ciprofloksacin	0	0	0
14.	Tigecyclin	0	0	0
15.	Nitrofurantoin	0	0	0
16.	Trimetoprim sulfametoxazol	0	0	0

The spread of resistance traits may occur, as resistance mechanisms can arise through genetic mutations, and these mutations can be transferred to other bacteria. (Wang, Y, 2024). The increasing incidence of resistance to carbapenem class antibiotics can further complicate the treatment of clinically relevant Enterobacteriaceae infections. Carbapenem-resistant Enterobacteriaceae are difficult to treat because they have developed broader resistance to carbapenems through the production and release of carbapenem-hydrolyzing  $\beta$ -lactamase enzymes (carbapenemases) or through structural mutations (Logan LK, 2017).

Carbapenems are one of the few treatments still available for *Enterobacteriaceae* that produce ESBLs so the use of carbapenems in Gram-negative bacilli infections that produce extended-spectrum beta-lactamase (ESBL) is increasing. The carbapenems are usually considered as last-line drugs, especially for the treatment of critically ill patients or those having a Gram-negative infection which is resistant to the majority of antibiotics. (Potter RF, 2016 ; Bialvaei, 2021). The increased consumption of antibiotics in clinical settings could also increase the

selection pressure of antibiotic resistance genes and may lead to high antimicrobial resistance rates. (Tadesse S, 2022).

## CONCLUSION

Multi-drug-resistant *Enterobacteriaceae* infections represent a serious concern to public health because of their high mortality rates. This study is expected to provide a clear picture of the prevalence of ESBL-producing and carbapenem-resistant bacteria at the hospital, those bacteria are *Escherichia coli* (50%) and *Klebsiella pneumoniae* (33,4%) and *Burkholderia cepacia* (16,6%). which can later be used to enhance surveillance and implement more effective antibiotic treatment policies. Understanding the prevalence and resistance patterns is important for the development of better antibiotic management policies and infection control strategies in hospitals. It is the right decision for the WHO, in the 2024 Update of the Bacterial Pathogen Priority List, to designate carbapenem-resistant *Enterobacteriaceae* with the highest score, confirming their inclusion in the critical priority category of the 2024 Bacterial Pathogen Priority List.

It is recommended to strengthen antimicrobial resistance stewardship through routine culture and susceptibility testing, rational use of antibiotics based on local antibiogram data, and strict monitoring of carbapenem prescriptions. Regular education of healthcare workers and periodic evaluation of antimicrobial use policies are also essential to prevent the emergence of resistant organisms.

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