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КЛІНІЧНА ПРАКТИКА

ОГЛЯД ЛІТЕРАТУРИ

НОВІ МЕТОДИ І ТЕХНОЛОГІЇ

ВИПАДОК ІЗ ЛІКАРСЬКОЇ ПРАКТИКИ

ФАРМАКОЛОГІЯ І ФАРМАЦІЯ

CONTENTS

THEORY AND EXPERIMENT

CLINICAL PRACTICE

LITERATURE REVIEW

NEW METHODS AND TECHNOLOGIES

A CASE FROM MEDICAL PRACTICE

PHARMACOLOGY AND PHARMACY

UDC 616.24-002.5:616.94:579.61:579.841:615.33:005.591.6
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MBL ENCODING GENES IN GRAM-NEGATIVE ESKAPE PATHOGENS FROM THE BLOODSTREAM OF ICU COVID-19 PATIENTS[1]

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Introduction. Severe COVID-19 cases face high risks of secondary bacterial infections and antimicrobial resistance due to prolonged hospital stays and heavy antibacterial use. Metallo-β-lactamases (MBLs) like VIM (Verona integron-encoded metallo-β-lactamase), IMP (imipenemase), and NDM (New Delhi metallo-beta-lactamase) confer broad resistance to β-lactams in Gram-negative ESKAPE pathogens, complicating intensive care unit (ICU) treatments and reducing survival rates. Rapid identification of these infections is crucial for critically ill patients.

Objective. The present study investigated β-lactamase genes in Gram-negative ESKAPE strains from COVID-19 ICU patients, focusing on MBL-producing strains.

Materials and methods. Blood samples were collected from ICU COVID-19 patients at Kharkiv's Regional Clinical Infectious Hospital, Ukraine, and analyzed using real-time PCR to detect MBL genes (VIM, IMP, NDM).

Results. MBL genes were identified in 43.6% of Gram-negative ESKAPE pathogens. NDM was found in 13.3%, VIM in 28.4%, and IMP in 1.9% of cases. *E. coli* showed a high incidence of MBL genes, while *P. aeruginosa* had the highest prevalence (72.2%). This reveals significant resistance levels that complicate ICU treatments.

Discussion. The high prevalence of MBL genes underscores the urgent need for advanced infection control and antimicrobial stewardship. Real-time PCR offers a rapid, effective method for identifying resistant strains, allowing healthcare facilities to take timely actions.

Conclusions. Carbapenem resistance in ESKAPE pathogens poses a serious challenge in ICU settings. High levels of MBL genes in bacteria like *E. coli* and *P. aeruginosa* raise concerns of interspecies resistance spread. Real-time PCR aids swift pathogen identification, essential for managing high-risk patients. Traditional infection control is insufficient; targeted approaches are needed. Agile infection control improves response and safety, helping manage antibiotic resistance.

Key words: Metallo-β-lactamases, ESKAPE pathogens, COVID-19, PCR, Agile.

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ГЕНИ MBL У ГРАМНЕГАТИВНИХ ESKAPE ПАТОГЕНІВ, ВИДІЛЕНИХ З КРОВІ COVID-19 ПАЦІЄНТІВ ВІДДІЛЕНЬ ІНТЕНСИВНОЇ ТЕРАПІЇ

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Пацієнти з тяжким COVID-19 мають високий ризик бактеріальних інфекцій і антимікробної резистентності через тривале перебування у стаціонарі. Метало-β-лактамази патогенів ускладнюють лікування, тож швидка ідентифікація таких інфекцій є критично важливою.

Мета роботи – дослідити MBL гени у грамнегативних ESKAPE патогенів від пацієнтів з COVID-19 у ВІТ. Проаналізовано зразки крові пацієнтів у Харківській інфекційній лікарні за допомогою ПЛР для виявлення грамнегативних ESKAPE патогенів та генів VIM, IMP, NDM. Гени MBL виявлено у 43,6% грамнегативних ESKAPE патогенів (13,3% – NDM, 28,4% – VIM, 1,9% – IMP).

Висновки. Карбапенемна резистентність у ESKAPE створює проблему у ВІТ. Поширеність генів MBL підвищує ризик передачі резистентності. ПЛР дозволяє швидко ідентифікувати стійкі штами. Необхідні цілеспрямовані стратегії контролю інфекцій, Agile-підхід покращує безпеку пацієнтів і персоналу.

Ключові слова: метало-β-лактамази, ESKAPE патогени, COVID-19, RT-PCR, Agile.

Introduction. Severe COVID-19 cases are associated with an increased risk of secondary bacterial infections due to prolonged hospital stays and weakened immune systems. The overuse of antibacterial drugs during the pandemic has led to a surge in antimicrobial resistance among bacterial pathogens [1–3].

Traditional blood culture methods have limitations in terms of speed and sensitivity and are affected by various factors that can reduce the chances of obtaining a positive result. The molecular epidemiology of β-lactamases is complex in both hospital and non-hospital environments, characterized by a high diversity of associated genes, mobile genetic elements, and plasmids, as well as diverse species composition and population structures among β-lactamase-producing strains [4; 5].

Metallo-β-lactamases (MBLs) are significant contributors to antibiotic resistance in Gram-negative bacteria. These enzymes confer resistance to nearly all β-lactams due to their broad substrate specificity, potent carbapenemase activity, and ability to resist inhibitors. MBL genes are located on mobile genetic elements, enabling their rapid spread among clinically important Gram-negative bacteria. Currently, the most effective and widely distributed carbapenemases are VIM (Verona integron-encoded metallo-β-lactamase), IMP (imipenemase), and NDM (New Delhi metallo-beta-lactamase) [6].

The presence of MBL-encoding genes is a critical prognostic factor for the ineffectiveness of empirical therapy against infections caused by ESKAPE pathogens. In severe infections, empirical antibiotic therapy fails in about one-third of cases, significantly increasing both mortality rates and hospital stays. Delays in administering appropriate antimicrobial therapy can compromise healthcare quality and exacerbate antimicrobial resistance [7].

Timely identification of bloodstream infections, especially those caused by ESKAPE pathogens, is vital in reducing the severe consequences of these infections, including high mortality risks. The ESKAPE pathogens represent a group of bacteria that are especially notorious for their resistance to multiple antibiotics, often leading to complex, hard-to-treat infections. This group is significant in healthcare settings due to its role in hospital-acquired infections and its capacity to "escape" the effects of standard antibiotic treatments [8]. The survival rate of patients with bloodstream infections, especially those caused by ESKAPE pathogens, heavily depends on rapid and accurate diagnosis, as there is an average 7.6% decrease in survival rate per hour from the onset of hypotension without effective antimicrobial treatment [9].

The study aimed to investigate the presence of specific β-lactamase genes in gram-negative ESKAPE strains from blood samples of COVID-19 patients admitted to Intensive Care Units (ICUs).

Materials and methods. Blood samples were collected from COVID-19 patients receiving critical care in the ICU at the Communal Non-commercial Enterprise of Kharkiv Regional Council "Regional Clinical Infectious Hospital" located in Ukraine. This hospital, known for handling infectious disease cases, became a central institution for treating severe COVID-19 patients requiring advanced medical support. These patients were admitted primarily due to severe respiratory issues associated with COVID-19, and their treatment often involved a multidisciplinary approach. Blood samples were collected specifically to study the occurrence and impact of bacterial bloodstream infections, as these can significantly worsen outcomes in critically ill patients. The study adhered strictly to the principles outlined in the Ethical Code of the World Medical Association (Helsinki Declaration).

Blood samples from patients were analyzed using the BIO-RAD CFX96 Real-Time PCR system and the RevoDx Sepsis Pathogen Detection Kit for the qualitative detection and identification of nucleic acids of bloodstream infection pathogens. Additionally, PCR was used to analyze genes encoding MBLs (VIM, IMP, NDM), as detailed in Table 1 [10]. Real-time PCR was chosen for its high sensitivity and accuracy in detecting pathogens even in trace amounts, which is crucial in managing infections in critically ill patients.

Whole blood samples were tested directly without the need for extensive culturing procedures, which is beneficial in urgent clinical settings where time is a factor. The identified pathogens included several bacteria from the *Enterobacteriaceae* family, specifically *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Escherichia coli*, all of which are commonly associated with severe infections in hospital environments. These pathogens are often resistant to a wide range of antibiotics, complicating

Table 1

Oligonucleotides utilized for detecting the acquired MBLs genes

Genes	Primer	Sequences 5'-3'	Amplicon	Annealing temp.
bla_{IMP}	IMP-F	GGAATAGAGTGGCTTAAYTCTC	232	52°C
	IMP-R	GGTTTAAYAAAACAACCACC		
bla_{VIM}	VIM-F	GATGGTGTTTGGTCGCATA	382	52°C
	VIM-R	CGAATGCGCAGCACCAG		
bl_{aND}M	NDM-F	GGTTTGGCGATCTGGTTTTC	621	52°C
	NDM-R	CGGAATGGCTCATCACGATC		

treatment strategies and contributing to prolonged ICU stays for patients. In addition to *Enterobacteriaceae* family members, gram-negative non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were also detected. These organisms are particularly challenging to treat due to their intrinsic resistance mechanisms, and they are prevalent in intensive care settings where patients often require prolonged ventilation and invasive monitoring. Their detection is crucial for guiding infection control practices and understanding the microbial landscape affecting COVID-19 patients in ICUs.

The study placed particular focus on identifying drug resistance genes associated with Ambler's class B beta-lactamases, including IMP, VIM, and NDM, as these genes are known contributors to high-level resistance against beta-lactam antibiotics, including carbapenems. Detecting these resistance genes is essential for epidemiological surveillance and informs clinicians about potential challenges in antimicrobial therapy.

Results. Genetic sequences responsible for MBLs were identified in 43.6% of all Gram-negative ESKAPE pathogens, as summarized in Table 2.

These MBLs are enzymes that provide bacteria with resistance against many beta-lactam antibiotics, including penicillins and carbapenems, making infections challenging to treat in clinical settings. Among the detected MBL genes, NDM was found in 13.3% of cases. NDM is particularly notable due to its association with high resistance levels and its rapid spread across various bacterial species, complicating infection control in healthcare environments. VIM was detected in 28.4% of cases, showing a relatively high prevalence and highlighting its significant role in antimicrobial resistance. IMP, on the other hand, was identified in 1.9% of cases, suggesting a lower but still relevant presence of this resistance gene within the studied pathogens.

In blood samples collected specifically from COVID-19 patients admitted to the ICU with bloodstream infections, 41.1% of *Enterobacteriaceae* strains were found to carry MBL genes. The prevalence of MBL genes within *Enterobacteriaceae* strains suggests a substantial level of resistance that could hinder effective antibiotic therapy in ICU settings.

E. coli showed the highest incidence of MBL genes among the strains identified, with VIM present in 40.4% of detected strains, indicating a significant prevalence of this resistance gene in this particular pathogen. *E. coli*, known to cause severe infections, is particularly concerning when it carries resistance genes, as it can rapidly spread within hospital environments and among immunocompromised patients.

In contrast, Gram-negative non-fermenting bacteria such as *P. aeruginosa* and *A. baumannii* demonstrated a higher overall proportion of MBL genes, with 66.7% of these bacteria carrying MBL genetic sequences. These non-fermenting bacteria are frequently implicated in hospital-acquired infections and tend to exhibit robust resistance profiles. Notably, *P. aeruginosa* exhibited an especially high prevalence of MBL genes, with 72.2% of detected strains carrying these resistance genes. The high occurrence of MBL genes in *P. aeruginosa* strains emphasizes its role as a challenging pathogen in ICU settings, as it often leads to persistent and difficult-to-treat infections.

This detailed breakdown highlights the significant presence of MBL genes among Gram-negative pathogens, especially in a vulnerable patient group like ICU COVID-19 patients, and underscores the importance of targeted infection control and antimicrobial stewardship to combat these resistant infections.

Discussion. Infections caused by gram-negative ESKAPE pathogens are associated with high mortality rates, especially in healthcare settings where they contribute to severe nosocomial diseases. Among these, bloodstream infections are particularly dangerous, requiring significant attention. Several factors elevate the risk of these infections, including prolonged hospital stays, intensive care unit admissions, invasive procedures, prior antibiotic usage, previous hospitalizations, residence in nursing homes, older age, and prior colonization by these pathogens [11]. ESKAPE pathogens produce carbapenemases, potent

Table 2

Prevalence of MBL-Encoding Genes in Gram-Negative ESKAPE pathogens

	***E. coli*, n=89**	***K. pneumonia*, n=83**	***A. baumannii*, n=3**	***P. aeruginosa*, n=18**	***E. cloacae*, n=18**	**Total MBLs**
IMP (n / %)	0	1/1.2	0	3/16.7	0	4/1.9
VIM (n / %)	36/40.4	13/15.7	1/33.3	9/50.0	1/5.6	60/28.4
NDM (n / %)	9/10.1	18/21.7	0	1/5.6	0	28/13.3

β-lactamases in various Ambler classes (A, B, C, D), which degrade many β-lactam antibiotics like carbapenems, cephalosporins, penicillins, and aztreonam. These enzymes are encoded by genes located in chromosomes or mobile genetic elements, heightening the risk of horizontal gene transfer to other bacterial species.

The prevalence of β-lactamase resistance genes among clinical ESKAPE isolates presents a serious infection control challenge, especially as there are currently no effective beta-lactamase inhibitors against MBL-producing pathogens. This study's detection of MBL genes is alarming, emphasizing the need for robust infection control practices. Traditional microbiological diagnostic methods often fall short in reliably detecting these resistance genes, as β-lactamase-producing strains may still appear susceptible by standard criteria [12]. In contrast, real-time multiplex PCR enables rapid genetic analysis of bacterial populations, identifying multiple DNA targets in a single sample, which helps clinicians and infection control specialists quickly identify high-risk patients.

To address these evolving nosocomial infection challenges, enhancing infection control in medical facilities is vital, necessitating regular updates to regulatory and methodological frameworks. This includes the thorough registration of infections, comprehensive data on pathogen resistance, and reinforcement of the hospital's epidemiological practices. Effective infection control is critical for preventing and managing nosocomial infections, as seen during the COVID-19 pandemic, where infection control measures were essential for safeguarding healthcare workers and patients and ensuring facility operations.

In this study, blood samples from COVID-19 ICU patients were analyzed using a multiplex real-time PCR technique to identify three specific types of carbapenemases (NDM, VIM, and IMP) within the MBLs class in Gram-negative ESKAPE pathogens. The findings showed that most bloodstream infections were caused by *Enterobacteriaceae*, with *E. coli* being the most common strain (89 isolates), followed by *K. pneumoniae* (83 isolates) and *E. cloacae* (18 isolates). While Gram-negative non-fermenters like *A. baumannii* (3 isolates) and *P. aeruginosa* (18 isolates) were not the primary culprits, their potential threat lies in the presence of MBLs genes on mobile genetic elements, posing a significant risk of horizontal gene transfer.

The study revealed that carbapenem resistance due to MBLs genes was present in 72.2% of *P. aeruginosa* isolates, 50.6% of *E. coli* isolates, 38.6% of *K. pneumoniae* isolates, 33.3% of *A. baumannii* isolates, and 5.6% of *E. cloacae* isolates. The high prevalence of MBL-producing Gram-negative bacteria in the study area indicates a potentially widespread issue. The detection of MBLs genes in Gram-negative ESKAPE pathogens underscores the importance of moving beyond traditional infection control methods to adopt clonally oriented measures aimed at limiting the spread of resistance genes.

Strategies for identifying and eliminating these genes are crucial. Additionally, enhancing the competence of healthcare professionals in the rational use of antibiotics through targeted training is essential. Infections caused by gram-negative ESKAPE pathogens can lead to notable mortality rates, particularly bloodstream infections, which are exacerbated by factors like extended hospital stays, intensive care, invasive procedures, and prior antibiotic use. These pathogens, especially those producing carbapenemases, represent a severe threat due to their resistance capabilities, with mobile genetic elements enabling horizontal gene transfer of β-lactamase resistance genes. Traditional diagnostic methods often fall short in identifying these resistance genes, whereas real-time multiplex PCR offers a promising approach for rapid detection, aiding infection control specialists in identifying high-risk patients swiftly. However, moving beyond traditional infection control is crucial, as the detection of MBLs genes in these pathogens demands clonally oriented measures to limit the spread of resistance, along with improved antibiotic stewardship through targeted healthcare training.

Agile transformation in infection control enhances efficiency and communication by promoting a collaborative, flexible approach [13]. This shift enables faster problem-solving, boosts staff engagement, and keeps practices aligned with current standards, which improves safety for both patients and staff. Although implementing Agile in conservative medical fields poses challenges, it optimizes the coordination and decision-making of specialists. Its flexibility allows medical institutions to quickly adapt to resistance trends, integrating real-time PCR findings and adjusting protocols accordingly. The Agile approach not only supports infection control in managing nosocomial infections but also significantly benefits healthcare quality and safety, ultimately improving treatment outcomes in medical facilities [14; 15].

Conclusions

1. The study highlights the pressing issue of carbapenem resistance in Gram-negative ESKAPE pathogens, with MBL-producing strains posing a significant challenge in ICU settings for COVID-19 patients.
2. The high prevalence of MBLs genes in bacteria like *E. coli*, *K. pneumoniae*, and *P. aeruginosa* suggests a serious potential for the spread of resistance through horizontal gene transfer, facilitated by mobile genetic elements.
3. Multiplex real-time PCR has proven effective for rapid detection of these resistance genes, allowing infection control specialists to act swiftly in identifying and managing high-risk patients.
4. Presence of MBL genes among Gram-negative pathogens, especially in a vulnerable patient group like ICU COVID-19 patients, and underscores the importance of targeted infection control and antimicrobial stewardship to combat these resistant infections. Agile transformation principles in infection control could support infection control in managing nosocomial infections as well as significantly benefits healthcare quality and safety, ultimately improving treatment outcomes in medical facilities.

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