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Original Research Article

Carbapenem resistance crisis: a retrospective investigation of gram-negative bacterial isolates in a tertiary care hospital in Egypt

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ABSTRACT

Background: The increasing prevalence of carbapenem-resistant gram-negative bacteria poses a significant threat to public health worldwide. This study aimed to investigate the patterns and determinants of carbapenem resistance among gram-negative bacterial isolates from patients admitted to Tanta University Chest Hospital, Egypt.
Methods: A retrospective, observational study was conducted, involving patients who received carbapenem antibiotics (ertapenem, imipenem, or meropenem) for at least 48 hours during their hospitalization between January 1, 2023, and December 31, 2023. Data on patient demographics, duration and indication of use and microbiological data were collected. Carbapenem resistance was assessed using antimicrobial susceptibility testing.
Results: A total of 80 patients with gram-negative bacterial cultures were included in the study. The overall prevalence of carbapenem resistance was 70%. No significant associations were found between carbapenem resistance and gender, age or indication. However, significant differences in resistance rates were observed among bacterial species. *Acinetobacter* (87%), *Klebsiella* (82%), and *Pseudomonas* (78%) exhibited high probabilities of carbapenem resistance, while *E. coli* had a lower resistance rate (31%). Logistic regression analysis confirmed that *E. coli* was significantly less likely to be resistant to carbapenems compared to *Pseudomonas* (p=0.039, OR=0.127, 95% CI: 0.018-0.905).
Conclusions: The study revealed an alarmingly high prevalence of carbapenem resistance among gram-negative bacterial isolates in a tertiary care hospital in Egypt. Effective antimicrobial stewardship programs, strict infection control measures, and continuous surveillance of antimicrobial resistance patterns are crucial to combat the growing threat of carbapenem-resistant organisms.

Keywords: Antimicrobial resistance, Bacterial species, Infection control, Risk factors

INTRODUCTION

The emergence and rapid dissemination of carbapenem-resistant Gram-negative bacilli (CR-GNB) pose a significant global public health threat. Carbapenems, a class of broad-spectrum β-lactam antibiotics, are often considered the last resort for treating infections caused by multidrug-resistant Gram-negative pathogens. However, the increasing prevalence of CR-GNB has severely limited therapeutic options and has been associated with higher morbidity, mortality, and healthcare costs.[1]

CR-GNBs are particularly problematic in healthcare settings, where they can cause a wide range of infections, including ventilator-associated pneumonia (VAP), bloodstream infections, urinary tract infections, and surgical site infections. The high mortality rates associated with these infections highlight the urgent need for effective

prevention and control strategies, as well as the development of novel therapeutic approaches.[2]

The resistance mechanisms exhibited by CR-GNB are diverse and complex, involving various enzymatic and non-enzymatic pathways. The production of carbapenemases, enzymes that can hydrolyze and inactivate carbapenems, is a significant contributor to carbapenem resistance. These carbapenemases belong to different molecular classes, such as class A (e.g., Klebsiella pneumoniae carbapenemase, KPC), class B (metallo-β-lactamases like New Delhi metallo-β-lactamase, NDM, and Verona integron-encoded metallo-β-lactamase, VIM), and class D (oxacillinases, OXA). Additionally, resistance can arise from alterations in outer membrane permeability, overexpression of efflux pumps, or a combination of these mechanisms.[3]

The molecular epidemiology of CR-GNB is of particular concern, as the resistance genes are often carried on mobile genetic elements, such as plasmids and transposons, facilitating their horizontal transfer among different bacterial species and strains. This genetic mobility has contributed to the rapid dissemination of CR-GNB across healthcare facilities and geographic regions, posing significant challenges for infection control efforts.[4]

The clinical implications of CR-GNB infections are grave, with limited treatment options and poor patient outcomes. Infections caused by these resistant pathogens are associated with increased mortality rates, prolonged hospital stays, and higher healthcare costs. Additionally, the emergence of extensively drug-resistant (XDR) and pan-drug-resistant (PDR) strains has further exacerbated the therapeutic challenges, leaving clinicians with few, if any, effective treatment options.[1]

Combating the threat of CR-GNB requires a multifaceted approach that encompasses various strategies, including antimicrobial stewardship, infection prevention and control measures, and the development of novel therapeutic interventions. Antimicrobial stewardship programs aim to promote the judicious use of antibiotics, reducing the selective pressure that drives the emergence and spread of resistant strains. Infection prevention and control measures, such as hand hygiene, environmental cleaning, and patient isolation, are crucial for limiting the transmission of CR-GNB within healthcare settings.[5]

Furthermore, the development of new antimicrobial agents, alternative therapeutic approaches (e.g., phage therapy, antimicrobial peptides), and improved diagnostic tools are actively being pursued to address the challenges posed by CR-GNB. Combination therapies, leveraging the synergistic effects of different antimicrobials or adjuvants, have also shown promise in overcoming resistance mechanisms and enhancing treatment efficacy.[6]

It is important to note that the burden of CR-GNB infections and the associated challenges vary across different geographic regions and healthcare settings. In resource-limited settings, where access to advanced diagnostic tools and newer antimicrobial agents may be limited, the impact of CR-GNB can be particularly severe. Therefore, a comprehensive understanding of the local epidemiology, resistance patterns, and risk factors is crucial for tailoring effective prevention and control strategies.[1]

METHODS

Study design and setting

This was a retrospective, observational study conducted at Tanta University Chest Hospital, Egypt.

Study population

The study population consisted of patients who were admitted to Tanta University Chest Hospital from 1st January 2023, to 31st December 2023 who received carbapenem antibiotics (ertapenem, imipenem, or meropenem) for at least 48 hours.

Inclusion criteria

Patients admitted to Tanta University Chest Hospital during the study period. Patients aged 18 years or older at the time of admission. Patients who received carbapenem antibiotics (ertapenem, imipenem or meropenem) for at least 48 hours during their hospitalization.

Exclusion criteria

Patients with incomplete or unavailable medical records or microbiology data essential for the study. Patients who were transferred from or to another healthcare facility during their hospital stay, as their complete antibiotic exposure and microbiological data may not be available. Patients who received carbapenem antibiotics solely for surgical prophylaxis.

Data collection

The following data was extracted from electronic medical records and microbiology laboratory databases: gender, age, underlying conditions, carbapenem utilization data (indication for use and duration of administration), microbiological data (culture results, antimicrobial susceptibility testing).

For patients with positive cultures, the following additional data will be collected: site of infection, organism(s) identified, antimicrobial susceptibility patterns.

Statistical analysis

The collected data was analyzed using SPSS statistical software. Descriptive statistics were used to summarize the

patient characteristics and clinical data. Categorical variables like gender, disease indications, and bacterial organisms were presented as frequencies and percentages. The t-test was used for numerical variables while chi-square test was used for categorical variables. Cross-tabulations were performed to compare the prevalence of carbapenem resistance among different bacterial species (*Acinetobacter*, *E. coli*, *Klebsiella*, *Pseudomonas*). Logistic regression analysis was carried out to identify bacterial species associated with higher odds of carbapenem resistance, using *Pseudomonas* as the reference category. A p value <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 101 patients were initially evaluated, of which 21 were excluded as they did not meet the inclusion criteria. The remaining 80 patients who received carbapenem and had gram-negative bacterial cultures were divided into two groups: resistant and non-resistant.

Table 1: Relationship between gender and carbapenem resistance.

Character	Data presentation	Resistant n=56	Not resistant n=24	P value
Sex	M:F	32:24	14:10	0.561
Age (years)	Mean±SD	58.04±15.9	62.38±16.2	0.285
Duration of use (day)	Mean±SD	10.27±2.9	10.26±2.5	0.992

Notes: Data presented as mean±SD for numerical data and as numbers for categorical data. M: Male, F: Female

Table 2: Relationship between carbapenem indication and resistance.

Indication	Not resistant (%)	Resistant (%)	Total	P value
Asthma	1 (25)	3 (75)	4	1.00
Asthma+ lung fibrosis	0 (0)	1 (100)	1	1.00
Asthma + COPD with RF II	0 (0)	1 (100)	1	1.00
Bilateral lung infiltrate	0 (0)	2 (100)	2	1.00
Bronchiectasis	1 (50)	1 (50)	2	1.00
Bronchogenic carcinoma	0 (0)	1 (100)	1	1.00
CAP	0 (0)	1 (100)	1	1.00
COPD	3 (21.3)	11 (78.6)	14	1.00
Fever	1 (100)	0 (0)	1	1.00
Post-intermittent hemodialysis	1 (50)	1 (50)	2	1.00
ILD	1 (100)	0 (0)	1	0.99
Left lung collapse	1 (100)	0 (0)	1	1.00
Left thalamic hematoma	0 (0)	1 (100)	1	0.99
Pneumonia	10 (31.3)	22(68.8)	32	1.00
Post covid fibrosis	0 (0)	1 (100)	1	1.00
Postictal	0 (0)	1 (100)	1	1.00
Pulmonary embolism	0 (0)	1 (100)	1	1.00
Pulmonary fibrosis	0 (0)	2 (100)	2	1.00
Rf type 2	0 (0)	2 (100)	2	1.00
Right sided lung mass	1 (50)	1 (50)	2	1.00
Right lung abscess	1 (100)	0 (0)	1	1.00
Sepsis	1 (100)	0 (0)	1	1.00
Septic emboli	0 (0)	1 (100)	1	0.99
Unknown	2 (50)	2 (50)	1	1.00

COPD: chronic obstructive pulmonary disease, RF: respiratory failure, CAP: community acquired pneumonia, ILD: interstitial lung disease. Data tested for significance using binary logistic regression test.

By comparing cases that have gram-negative bacteria that are resistant to carbapenem (56 case) and do not resist (24 case) by using a one-sample binomial test. The overall prevalence of carbapenem resistance was 70% which considered statistically significant (p value =0.001).

Table 1 shows that there was no significant relationship between gender, age or duration of treatment and carbapenem resistance (p>0.05).

Data tested for significance using independent sample t-test for numerical data and chi square for categorical one.

Table 2 displays the distribution of diseases among patients with and without carbapenem resistance. By using logistic regression testing show that there was no significant association found between disease or indication and carbapenem resistance (p>0.05).

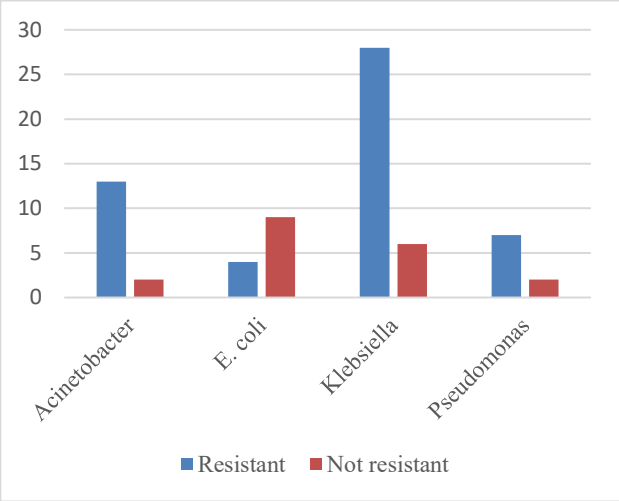

Figure 1: Association between type of gram-negative bacteria and carbapenem resistance.

Gram-negative isolates obtained from cultures were further compared to show percentage resistance among each isolated microorganism. Notably, *Acinetobacter*, *Klebsiella*, and *Pseudomonas* exhibited high probabilities of carbapenem resistance (87%, 82%, and 78%, respectively), while *E. coli* had a lower resistance rate (31%). Logistic regression analysis confirmed that *E. coli* was significantly less likely to be resistant to carbapenems compared to Pseudomonas (p=0.039, OR=0.127, 95% CI: 0.018-0.905) as shown in Figure 1.

DISCUSSION

This retrospective observational study investigated the prevalence and patterns of carbapenem resistance among gram-negative bacterial isolates from patients admitted to Tanta University Chest Hospital, Egypt. The findings revealed a high rate of carbapenem resistance (70%) among the gram-negative bacterial isolates, which is consistent with the growing global concern over the rise of carbapenem-resistant organisms.[7]

The study did not find a significant association between gender and carbapenem resistance, which aligns with previous reports suggesting that gender is not a major determinant of carbapenem resistance.[8] However, gender significantly influences the development and expression of carbapenem-resistance genes in bacteria.[9] Studies have shown that carbapenem-resistant *E. coli* isolated from female patients exhibited a high prevalence of resistance genes like blaNDM-1 and blaOXA-48.[10] Additionally, the expression of the New Delhi Metallo-β-lactamase-1 gene (blaNDM-1) was evaluated in clinical isolates, revealing altered expression patterns when exposed to imipenem, indicating a gender-related impact on resistance development.[11] Overall, gender influences the prevalence, expression, and stability of carbapenem-resistance genes in bacteria, underscoring the importance of considering gender dynamics in antimicrobial resistance research.

Interestingly, the disease indications for which patients were admitted did not show a significant relationship with carbapenem resistance. This finding suggests that carbapenem resistance is likely influenced by other factors, such as prior antibiotic exposure, infection control practices, and specific resistance mechanisms within the bacterial population.[12]

The high prevalence of carbapenem resistance observed in this study is concerning and aligns with the global trend of increasing antimicrobial resistance (AMR) rates. The overuse and misuse of antibiotics, particularly in healthcare settings, are major contributing factors to the emergence and spread of resistant bacteria.[13,14] Additionally, poor infection control practices, such as inadequate hand hygiene and improper isolation of infected patients, can facilitate the transmission of resistant organisms within healthcare facilities.[15]

The study found significant differences in carbapenem resistance rates among different bacterial species. *Acinetobacter*, *Klebsiella*, and *Pseudomonas* exhibited high probabilities of carbapenem resistance (87%, 82%, and 78%, respectively), while *E. coli* had a lower resistance rate (31%). These findings are consistent with previous reports indicating that *Acinetobacter*, *Klebsiella*, and *Pseudomonas* species are among the most common carbapenem-resistant pathogens worldwide.[9]

The lower resistance rate observed in *E. coli* compared to other gram-negative bacteria could be attributed to several factors. Firstly, *E. coli* is a more common cause of community-acquired infections, where carbapenem usage is typically lower than in hospital settings.[16] Additionally, the resistance mechanisms involved in carbapenem resistance, such as the production of carbapenemases or the combined activity of extended-spectrum β-lactamases (ESBLs) and porin mutations, may be less prevalent in *E. coli* isolates compared to other gram-negative species.[17,18]

The high rates of carbapenem resistance observed in this study highlight the urgent need for implementing effective antimicrobial stewardship programs and infection control measures within healthcare facilities. Strategies such as promoting judicious antibiotic use, improving hand hygiene compliance, and implementing active surveillance and isolation protocols for resistant organisms can help mitigate the spread of carbapenem-resistant pathogens.[19] Furthermore, continuous monitoring of antimicrobial resistance patterns and the implementation of robust diagnostic tools for the early detection of resistance mechanisms are crucial for guiding appropriate

antimicrobial therapy and preventing the further dissemination of resistant strains.[20]

It is important to note that this study was conducted in a single hospital setting, and the results may not be generalizable to other healthcare facilities or regions. Additionally, the retrospective nature of the study and the potential for incomplete or missing data could introduce limitations. Future prospective studies involving multiple healthcare centers and a larger sample size would provide more comprehensive insights into the epidemiology and risk factors associated with carbapenem resistance in Egypt.

Overall, this study highlights the alarming prevalence of carbapenem resistance among gram-negative bacterial isolates in a tertiary care hospital in Egypt. The findings emphasize the need for robust antimicrobial stewardship programs, strict infection control measures, and continuous surveillance of antimicrobial resistance patterns to combat the global threat of carbapenem-resistant organisms.

CONCLUSION

The study revealed an alarmingly high prevalence of carbapenem resistance among gram-negative bacterial isolates in a tertiary care hospital in Egypt. Effective antimicrobial stewardship programs, strict infection control measures, and continuous surveillance of antimicrobial resistance patterns are crucial to combat the growing threat of carbapenem-resistant organisms.

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