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Escherichia coli and MSSA urinary tract infections: Carbapenem de-escalation challenges and outcomes

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ABSTRACT

This retrospective study evaluated carbapenem de-escalation in urinary tract infection patients with *Escherichia coli* (*E. coli*) or Methicillin-sensitive Staphylococcus aureus (MSSA) at Jordan University Hospital from January 2019 to July 2021. Among 398 patients who received empiric carbapenem therapy, 94 (23.6%) had positive urine cultures. Specifically, 67 patients had *E. coli*, 11 had MSSA, and 16 had both pathogens, with most (83%) having infections with a single organism. Only 9.6% of patients underwent successful de-escalation to a narrower-spectrum antibiotic within 48 hours of culture results, while 2.1% were incorrectly de-escalated. Interestingly, those who were successfully de-escalated had a longer median hospital stay (27 days, inter-quartile range [IQR] = 24) compared to those who failed or were incorrectly de-escalated (median = 9 days, IQR = 10) (p = 0.004). The low rate of de-escalation may reflect physicians' reluctance to switch from broad-spectrum to narrow-spectrum antibiotics. Additionally, the longer hospital stays associated with successful de-escalation suggest the presence of underlying clinical factors influencing physicians' behavior.

Keywords: urinary tract infection, carbapenem, de-escalation, *Escherichia coli*, methicillin-sensitive *Staphylococcus aureus*

INTRODUCTION

Urinary tract infections (UTIs) present a significant load on healthcare systems, affecting millions worldwide each year [1, 2]. *Escherichia coli* (*E. coli*) and *Methicillin-sensitive Staphylococcus aureus* (MSSA) are among the leading pathogens responsible for these infections [3, 4]. Appropriate administration of both empiric and targeted treatments for UTIs not only improves clinical outcomes but also reduces morbidity and mortality [5]. Furthermore, the selection of targeted treatment should be guided by the results of culture and susceptibility testing [6]. This approach guarantees that antibiotics are tailored to the particular bacterium causing the UTI, thereby maximizing efficacy while minimizing the risk of antimicrobial resistance development [7].

Carbapenems, a class of β-lactam antibiotics, are commonly prescribed for empiric therapy due to their unparalleled broad spectrum of activity against the majority of Gram-negative bacteria, including multidrug-resistant organisms such as extended-spectrum β-lactamase-producing *Enterobacteriaceae*, *Pseudomonas aeruginosa,* and *Acinetobacter baumanni* [8]. This versatility makes carbapenems the preferred treatment for treating severe, multidrug-resistant, and complicated infections [9]. However, prolonged and escalated use of carbapenems can result in the emergence and spread of drug-resistant bacteria, increasing the possibility of infection with drug-resistant Gram-negative bacteria [10].

The Centers for Disease Control and Prevention have identified infections caused by carbapenem-resistant *Enterobacteriaceae* as a major threat to human life and health [9]. Similarly, the World Health Organization has confirmed the necessity of developing novel agents against these infections [11]. Despite efforts to combat them, these resistant gram-negative organisms commonly present as UTIs, including acute pyelonephritis, with a mortality rate ranging from 20 to 54.3% [12]. Furthermore, in line with these considerations, international guidelines promote the implementation of antibiotic de-escalation as a cornerstone approach within antimicrobial stewardship programs [13, 14].

Antibiotic de-escalation involves terminating one or more combination empirical antimicrobials or substituting a broad-spectrum antimicrobial with a more targeted agent [15]. For

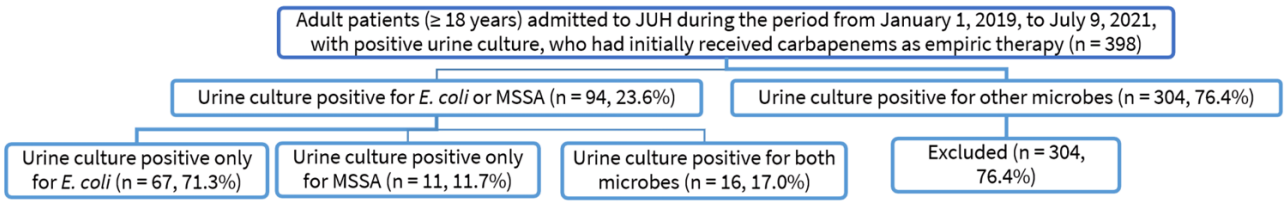

Figure 1. Flowchart of patient selection (Source: Authors' own elaboration)

instance, in cases where carbapenems are initially administered empirically for UTIs, a targeted de-escalation strategy can be implemented once culture and susceptibility results become available [14, 16]. If the identified pathogen demonstrates susceptibility to antibiotics with a narrow spectrum, such as cephalosporins or penicillins, carbapenem therapy can be appropriately de-escalated [17]. This targeted approach optimizes treatment effectiveness while simultaneously alleviating the selective pressure on carbapenems [16]. Consequently, it mitigates the risk of developing carbapenem-resistant organisms and associated with adverse effects [16]. Furthermore, de-escalation of therapy has resulted in a reduction in both antibiotic prescription rates and the duration of hospital admissions [13, 18, 19].

The existing literature predominantly targets de-escalation therapy in seriously ill patients, demonstrating its safety and association with reduced mortality rates [20-23]. However, there is limited reporting on the impact of de-escalation strategies on patients with UTIs, particularly those caused by *E. coli* or MSSA. Thus, the primary aim of this study was to evaluate the prevalence of carbapenems de-escalation in UTI patients infected with *E. coli* or MSSA in a tertiary teaching hospital in Jordan.

MATERIALs AND METHODS

Study Design and Study Subjects

This retrospective observational study aimed to assess the prevalence of carbapenem de-escalation among hospitalized UTI patients with positive culture reports of *E. coli* or MSSA. The study took place at Jordan University Hospital (JUH), the first academic teaching hospital in Jordan, with a bed capacity of 550. The inclusion criteria encompassed adult patients (≥ 18 years) admitted to JUH during the period from January 1, 2019, to July 9, 2021, diagnosed with UTI, who had initially received carbapenems as empiric therapy, and whose microbiological cultures yielded positive results for *E. coli* or MSSA. Exclusion criteria included negative microbiological cultures, absence of culture requests, and cases with multiple or unknown sources of infection.

Data Collection

Data extraction from electronic clinical records included gathering various patient information such as age, gender, admission and discharge dates, length of hospital stay, number of chronic medications, as well as details regarding prescribed empiric antibiotics and targeted therapy. Additionally, data pertaining to urine culture and susceptibility reports were sourced from the laboratory's electronic system at JUH.

Carbapenem De-Escalation

Successful carbapenem de-escalation was defined as the substitution of the carbapenem with a narrower spectrum antimicrobial agent within 48 hours of culture reports [24]. Successful de-escalation was characterized by the initiation of de-escalation within 48 hours of culture reports. Failure to de-escalate occurred if carbapenems were continued post-positive culture reports of *E. coli* or MSSA, substituted with another carbapenem, replaced by a different broad-spectrum antibiotic, or de-escalated after the 48-hour timeframe.

Ethical Consideration

The study adhered to the guidance outlined in the World Medical Association Declaration of Helsinki [25]. It commenced after receiving approval from the Institutional Review Board Committee on JUH, with reference number 196/2021. To ensure confidentiality and data security, all collected information was stored on the personal computer of the principal investigator using password-protected files.

Statistical Analysis

All collected data underwent coding, entry, and analysis using the statistical package for social sciences version 22. Descriptive analysis was conducted, summarizing continuous variables with median and interquartile range, and categorical variables were presented as percentages. Checking for normality was performed using the Shapiro-Wilk test, with a significance level set at $p \leq 0.05$. A result of $p \leq 0.05$ would indicate that our continuous variables were not normally distributed. The effect of de-escalation on hospital length of stay was evaluated using a two-tailed Mann-Whitney U test. A significance level of $p \leq 0.05$ was employed, indicating statistical significance.

RESULTS

During the study period, carbapenems were prescribed as empiric antibiotics for UTI to 398 patients (**Figure 1**). Among them, 94 patients (23.6%) tested positive for either *E. coli* or MSSA and were consequently included in the study. Specifically, 67 patients (71.3%) tested positive for *E. coli* alone, 11 tested positives for MSSA alone (11.7%), and 16 (17.0%) tested positive for both microbes.

The median age of the participants was 69 years (with an interquartile range of 21), and 51.1% (48 participants) were female. Additionally, over half of the patients (58 individuals, 61.7%) were receiving polypharmacy, defined as being prescribed four or more medications. The median length of hospital stay for these patients was 11 days (with an interquartile range of 12). Further details regarding the demographic and medical characteristics of the study sample are provided in **Table 1**.

Table 1. Demographic and medical characteristics of the study sample (n = 94)

Parameter		Median (IQR)	n (%)
Age in years		69.0 (21.0)	
Gender	Female		48 (51.1)
	Male		46 (48.9)
Number of chronic medications	0-1		12 (12.8)
	2-3		24 (25.5)
	≥ 4		58 (61.7)
Length of stay		10.5 (12.0)	

Table 2. Overview of empiric antibiotics prescribed prior to urine culture results in the study cohort (n = 94)

Parameter		n (%)
Number of prescribed antibiotics per patient	One	67 (71.3)
	Two	23 (24.5)
	Three	4 (4.3)
Total number of antibiotics prescribed		125
Total number of carbapenems prescribed		94
Type of carbapenem prescribed	Imipenem/cilastatin	66 (70.2)
	Ertapenem	21 (22.3)
	Meropenem	7 (7.4)

The total number of prescribed empiric antibiotics for those with positive urine cultures of *E. coli* or MSSA was 125, of which 94 were carbapenems as shown in **Table 2**. A majority of patients were administered with a single antibacterial agent (n = 67, 71.3%), while 24.5% received two antibacterial agents (n = 23), and only 4.3% were given to three antibacterial agents (n = 4). Imipenem/cilastatin emerged as the most commonly prescribed carbapenem (n = 66, 70.2%), followed by ertapenem (n = 21, 22.3%) and meropenem (n = 7, 7.4%).

Information regarding urine culture and susceptibility testing is provided in **Table 3**. The majority of urine culture specimens indicated the presence of a single microorganism (n = 78, 83.0%), while a smaller portion exhibited two pathogens (16, 17.0%). *E. coli* was the sole microorganism detected in the cultures of 67 patients (71.3%), whereas MSSA was found alone in the cultures of 11 patients (11.7%). Additionally, 16 patients had both *E. coli* and MSSA in their cultures (n = 16, 17.0%). Furthermore, more than half of the patients (n = 54, 57.4%) underwent susceptibility testing, revealing that only two patients displayed resistance to carbapenem (mainly imipenem) (2/54, 3.7%).

Table 3. Summary of urine culture and susceptibility reports in the study cohort (n = 94)

Parameter		n (%)
Number of microorganisms per specimen	One	78 (83.0)
	Two	16 (17.0)
Type of microorganism identified per specimen	*E. coli* only	67 (71.3)
	MSSA only	11 (11.7)
	Both *E. coli* and MSSA	16 (17.0)
The availability of susceptibility reporting	No	40 (42.6)
	Yes	54 (57.4)
Number of patients with resistant microorganisms		2/54 (3.7)

Of the 94 carbapenem prescriptions identified during the study period, successful de-escalation to narrower spectrum antibiotics occurred in 9 patients (9.6%) within 48 hours of urine culture results. Two patients (2.1%) underwent incorrect de-escalation by discontinuing antibiotic treatment despite positive urine culture results. The remaining 83 patients (88.3%) did not undergo carbapenem de-escalation, either by continuing the same treatment (n = 74, 78.7%), switching to another carbapenem (n = 8, 8.5%), or transitioning to gentamicin (n = 1, 1.1%). Further details on carbapenem de-escalation are provided in **Table 4**.

When assessing the impact of successful carbapenem de-escalation on patients' length of hospital stay using the Mann-Whitney U test, unexpected findings emerged (**Table 5**). Patients who underwent successful de-escalation exhibited a significantly longer length of stay (median = 27 days, inter-quartile range [IQR] = 24) compared to those who experienced failed de-escalation or incorrect de-escalation of carbapenem (median = 9 days, IQR = 10) (p = 0.004).

DISCUSSION

Carbapenems are crucial in combating multidrug-resistant bacteria, and the emergence of carbapenem resistance is a serious threat to healthcare [26-28]. Therefore, there is a need for new and effective strategies to counteract resistance, such as combination therapy and other antimicrobial alternatives [29, 30]. One of the important strategies to reduce carbapenem and other broad-spectrum antibiotic resistance is to reduce the unnecessary of carbapenems by switching from these broad-spectrum antibiotics to narrow-spectrum antibiotics as soon as

Table 4. Carbapenem de-escalation following positive urine culture report of *E. coli* or MSSA (n = 94)

Antibiotic before culture report	Antibiotic after culture report of *E. coli* or MSSA	The evaluation of antibiotic change[a]
Imipenem/cilastatin (66 patients)	Imipenem/cilastatin (51 patients)	Failed de-escalation
	Meropenem (3 patients)	Failed de-escalation
	Ertapenem (2 patients)	Failed de-escalation
	Gentamicin (1 patient)	Failed de-escalation
	Levofloxacin (3 patients)	Successful de-escalation
	Vancomycin (1 patient)	Successful de-escalation
	Levofloxacin + vancomycin (1 patient)	Successful de-escalation
	Ceftriaxone (1 patient)	Successful de-escalation
	Linezolid (1 patient)	Successful de-escalation
	No treatment (2 patients)	Incorrect de-escalation
Ertapenem (21 patients)	Ertapenem (18 patients)	Failed de-escalation
	Imipenem/cilastatin (1 patient)	Failed de-escalation
	Meropenem (1 patient)	Failed de-escalation
	Piperacillin (1 patient)	Successful de-escalation
Meropenem (7 patients)	Meropenem (5 patients)	Failed de-escalation
	Imipenem/cilastatin (1 patient)	Failed de-escalation
	Levofloxacin (1 patient)	Successful de-escalation

Note. [a]The evaluation of changes was conducted following consideration of both the identified pathogen and the antimicrobial spectrum of action

Table 5. Assessing the impact of successful carbapenem de-escalation on patients' length of hospital stay using the Mann-Whitney U test (n = 94)

Outcome	Successful de-escalation (n = 9)	Failed de-escalation/incorrect de-escalation (n = 83)	p-value
Length of stay (days), median (IQR)	27.0 (24.0)	9.0 (10.0)	0.004

the susceptibility results are available and if appropriate alternatives are present and it is feasible [31]. International guidelines promote antibiotic de-escalation, among other measures, as part of an antimicrobial stewardship program aimed to reduce resistance [14, 15].

In this study, almost half of the patients did not have susceptibility reports; hence, there was no information on carbapenem resistance in these patients. Carbapenem resistance is low in the patients with identified susceptibility reports (3.7%). Globally, reports from different studies showed higher incidence. In Iran, it was revealed that 56.3% of *P. aeruginosa* isolates were carbapenem-resistant [32], 27.5% in Taiwan [33], and 52% in Vietnam [34]. Results concerning the incidences and prevalence of carbapenem resistance should be interpreted with caution since studies differ in the clinical setting, microorganisms, and type of isolates.

Even after susceptibility results, successful carbapenem de-escalation was very limited, 9.6%. The process of de-escalation is crucial in infectious diseases since there is a need to narrow down the spectrum of antibiotics and use those that are effective against the specific microorganism after the susceptibility results are acquired. This reduces exposure to carbapenem and consequently reduces the risk of resistance [35]. However, de-escalation can have drawbacks. The study in [36] showed that patients who were switched from carbapenems to other antibiotics needed longer duration of antibiotic therapy.

In our study, successful de-escalation was characterized by the initiation of de-escalation within 48 hours of culture reports. Still, usually, it takes 48-72 hours until susceptibility results are available after isolation. Viasus et al., de-escalation therapy was performed after 72 hours in hospitalized patients with community-acquired pneumococcal pneumonia [37].

Patients who underwent successful de-escalation exhibited a significantly longer length of stay (median = 27 days, IQR = 24) compared to those who experienced failed de-escalation or incorrect de-escalation of carbapenem (median = 9 days, IQR = 10). This is contrary to the study in [38] that assessed the safety and efficacy of carbapenem de-escalation and its effect on clinical outcomes. The findings from the study revealed that the hospital stay of de-escalated patients was 6 days shorter compared to other patients [38]. Similarly, it was reported that de-escalation shortened the length of hospital stay [37]. A possible explanation of the longer hospital stay in our study is that clinicians do not trust narrow-spectrum antibiotics and believe that switching from a broad-spectrum to a narrow-spectrum antibiotic necessitates a longer treatment period, leading to a longer hospital stay. However, despite the longer hospital stay, de-escalation guided by an antimicrobial stewardship program has proven in other studies to be beneficial by reducing adverse drug reactions, *Clostridium difficile* associated diarrhea, and carbapenem-resistance [39].

This is the first study in Jordan to evaluate the prevalence of carbapenem de-escalation in UTI patients infected with *E. coli* or MSSA and its impact on patients' hospital stay. This issue is important since Jordan is a developing country with limited and overwhelmed healthcare services. It also sheds light on the low rate of carbapenem de-escalation among physicians, which might reflect a lack of knowledge of appropriate narrow-spectrum antimicrobials to switch to or ignorance of the important role of de-escalation in reducing resistance and other clinical outcomes. Physicians should be encouraged to enroll in antimicrobial stewardship, and awareness campaigns should be conducted to address worries that healthcare providers might have in the de-escalation of antibiotics.

The study has several limitations, such as the retrospective design and the absence of any information not available in the electronic records, such as the history of antibiotic therapy and the history of resistant microorganisms that might hinder a successful de-escalation. In this study, we did not explore the effect of de-escalation among other variables that might affect the length of hospital stay. In addition, this is a single-center study, and the generalizability of the results to other medical institutions could be compromised.

CONCLUSION

Successful carbapenem de-escalation is not a common practice and is associated with a longer hospital stay. This may be attributed to physicians' hesitation in transforming patients from broad-spectrum antibiotics to narrow-spectrum antibiotics. Reasons for this hesitation may be being unaware of the importance of de-escalation in reducing resistance and the numerous other benefits. Moreover, patients who underwent carbapenem de-escalation had longer hospital stays, contrary to many studies which suggest the presence of clinical disparities that affect the physicians` behavior. Participation in antimicrobial stewardship and educational activities that tackle this issue is necessary to provide physicians with the confidence needed and information on the conduction of successful carbapenem de-escalation.

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AI statement: The authors stated that generative AI was used solely to assist with language editing. All content, analyses, interpretation, and conclusions are the original work of the authors.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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