ORIGINAL ARTICLE

Oral treatment options for patients with urinary tract infections caused by carbapenem-resistant *Escherichia coli*

Nasrullah Malik[1], Aqib Sultan[1], Farah Shameem[2], Summiya Nizamuddin[1]

[1]Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore Pakistan
[2]Wah Medical College, Wah Cantt Pakistan

ABSTRACT

Background: Urinary tract infections (UTIs) are prevalent globally, with *Escherichia coli* being the predominant pathogen. Carbapenem-resistant *E. coli* strains exacerbate the clinical burden due to restricted treatment options. This study assessed the antibiotic susceptibility profiles of carbapenem-resistant *E. coli* strains associated with UTIs, aiming to identify effective oral treatment alternatives.

Material and Methods: The Cross-sectional study was conducted in the section of microbiology of the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from January 2018 to December 2022. This study was undertaken to assess the prevalence of carbapenem-resistant *E. coli* in urine samples and their susceptibility profiles against fosfomycin, nitrofurantoin, co-trimoxazole, ciprofloxacin, and tetracycline.

Results: A total of 978 carbapenem-resistant *E. coli* isolates were identified during this time period. Approximately 54% (527) of these isolates were recovered from female patients. Fosfomycin, nitrofurantoin, tetracycline, cotrimoxazole and ciprofloxacin were found to be susceptible against 82%, 67.2%, 15.2%, 9.7% and 0.1% carbapenem-resistant *E. coli* isolates, respectively. More than 80% of all *E. coli* were sensitive to fosfomycin. Ciprofloxacin exhibited the lowest susceptibility rate. 82% of carbapenem-resistant *E. coli* isolates were susceptible to fosfomycin, 67.2% to nitrofurantoin, 15.2% to tetracycline, 9.7% to cotrimoxazole, and 0.1% to ciprofloxacin.

Conclusion: The emerging carbapenem resistance among gram-negative bacteria markedly limits oral therapeutic alternatives. However, this study displays high susceptibility rates to fosfomycin and nitrofurantoin. We propose their utilization for managing uncomplicated UTIs caused by carbapenem-resistant *E. coli*.

Keywords: Carbapenem resistance, *Escherichia coli*, Urinary tract infections

BACKGROUND

Urinary tract infections (UTIs) stand out as one of the most prevalent infectious diseases, affecting individuals in both community and hospital settings, thereby contributing significantly to the healthcare burden.[1] UTIs exhibit a higher incidence in females a phenomenon attributed to the relatively shorter length of their urethras in comparison to males.[2]

Correspondence: Dr. Aqib Sultan, Resident Microbiology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

Email: aqib.cmh@gmail.com

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Cystitis and other lower urinary tract infections are often managed in outpatient settings. Whereas, upper UTIs such as pyelonephritis often entail the risk of sepsis and bacteremia, necessitating the administration of intravenous antibiotics and hospitalization for effective treatment.[3]

Gram-negative bacteria constitute the predominant etiological agents of UTIs, comprising of more than 90% of reported cases. Among these, *Escherichia coli* (*E. coli*) emerges as the most prevalent gram-negative bacterium responsible for UTIs, contributing to approximately 80% of all occurrences.[4]

The escalation of antimicrobial resistance within the Enterobacterales group has presented a difficult challenge in the treatment of UTIs, primarily stemming from the restricted options of available therapeutic alternatives. The global emergence of Enterobacterales capable of producing extended spectrum beta-

lactamases (ESBL) had exacerbated this issue, resulting in the ineffectiveness of commonly prescribed oral antibiotics like trimethoprim, quinolones, cephalosporins, and penicillins for the management of UTIs.[5]

Further on, with the advent of carbapenem resistance, managing these infections with limited treatment options has become a global challenge. Carbapenem-resistant strains also present a significant public health menace, given their propensity for extensive dissemination, resulting in elevated morbidity and mortality rates within healthcare setting.[6] UTIs attributed to carbapenem-resistant Enterobacterales also correlate with prolonged hospitalization durations and escalated healthcare costs.[7]

The search for novel antibiotics is desperately needed. The revival of old antimicrobials like, fosfomycin, and nitrofurantoin could offer a valuable solution in this scenario, bridging the gap until the development of novel antimicrobials.[8]

Fosfomycin is an oral bactericidal drug, having antimicrobial properties against both gram-positive and gram-negative organisms, and has been used to treat UTIs for the last four decades. Nitrofurantoin is another oral bactericidal drug, considered as the first line therapy for acute uncomplicated UTI.[9]

Co-trimoxazole, ciprofloxacin and doxycycline are also other oral antibiotic options available for treating UTIs, however, these are usually opted for as targeted therapy choices, as opposed to being prescribed empirically.[10]

The selection of an effective oral antibiotic therapy may be aided by knowledge of the local prevalence of carbapenem-resistant *E. coli* that causes UTIs and their drug susceptibility profile. This retrospective study was therefore carried out to evaluate the antibiotic susceptibility profiles of carbapenem-resistant *E. coli* stains, in order to identify the effective oral treatment options.

MATERIAL AND METHODS

This retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Lahore. Urine culture and susceptibility data from SKMCH & RC, Lahore and its network of laboratory collecting centers across Pakistan were analyzed. All carbapenem-resistant *E. coli* isolates recovered from urine cultures between January 2018 and December 2022 were included in this study, while carbapenem-susceptible *E. coli* isolates and duplicate isolates were excluded. *E. coli* isolates found to be resistant to imipenem, meropenem, ertapenem or doripenem according to the current Clinical and Laboratory Standards Institute (CLSI) M100, 33rd edition breakpoints (unchanged since 2011) were defined as carbapenem-resistant (11).

Using a semi-quantitative method, urine samples collected from patients either midstream or by catheterization were cultured onto Cystine Lactose Electrolyte Deficient (CLED) agar using 0.01 mL calibrated loops. Culture plates were incubated for 24 hours at 37 °C. Conventional techniques like API (BioMeurex) were utilized to identify the isolated microorganisms.

Antimicrobial susceptibility testing was done by the disc diffusion method according to CLSI M100, 33rd edition guidelines.[11]

Data on the patient's demographics, laboratory results, and susceptibility results for fosfomycin, nitrofurantoin, trimethoprim, ciprofloxacin, and tetracycline were obtained from the hospital information management system. No clinical data was gathered.

All clinical and microbiological data was compiled and analyzed using Statistical Package for Social Sciences (SPSS) version 24.0. Descriptive statistics were presented in the form of frequencies and percentages. Frequencies of susceptibility rates of fosfomycin, nitrofurantoin, co-trimoxazole, ciprofloxacin and tetracycline against carbapenem-resistant *E. coli* were represented by using percentages and graphs.

RESULTS

From 2018 to 2023, a total of 13,332 *Escherichia coli* isolates were obtained from urine cultures. Among these, 978 isolates were identified as carbapenem-resistant and were included in this study. Of these carbapenem-resistant isolates, 527 (53.9%) were from female patients and 451 (46.1%) from male patients. The mean age of patients was 50 years. Specifically, 462 (47.2%) isolates were from patients aged 19-64 years, 413 (42.2%) from patients older than 64 years, and 103 (10.5%) from patients 18 years old or younger.

The majority of 757 isolates (77.4%) originated from Punjab, followed by 181 isolates (18.5%) from Khyber

Pakhtunkhwa, 17 isolates (1.7%) from the Federally Administered Tribal Areas (FATA), 10 isolates (1%) from Balochistan, 9 isolates (0.9%) from Sindh, and 4 isolates (0.4%) from Azad Jammu and Kashmir.

Antimicrobial susceptibility testing of carbapenem-resistant *E. coli* showed that the bulk of the isolates were susceptible to fosfomycin and nitrofurantoin, with fosfomycin susceptibility at 82% (802) and nitrofurantoin susceptibility at 67.2% (657).

Simultaneously, these isolates showed poor susceptibility to tetracycline, co-trimoxazole and ciprofloxacin. Only 152 (15.5%) isolates were susceptible to tetracycline, 95 (9.7%) isolates were susceptible to co-trimoxazole, and 23 (2.4%) isolates showed susceptibility to ciprofloxacin.

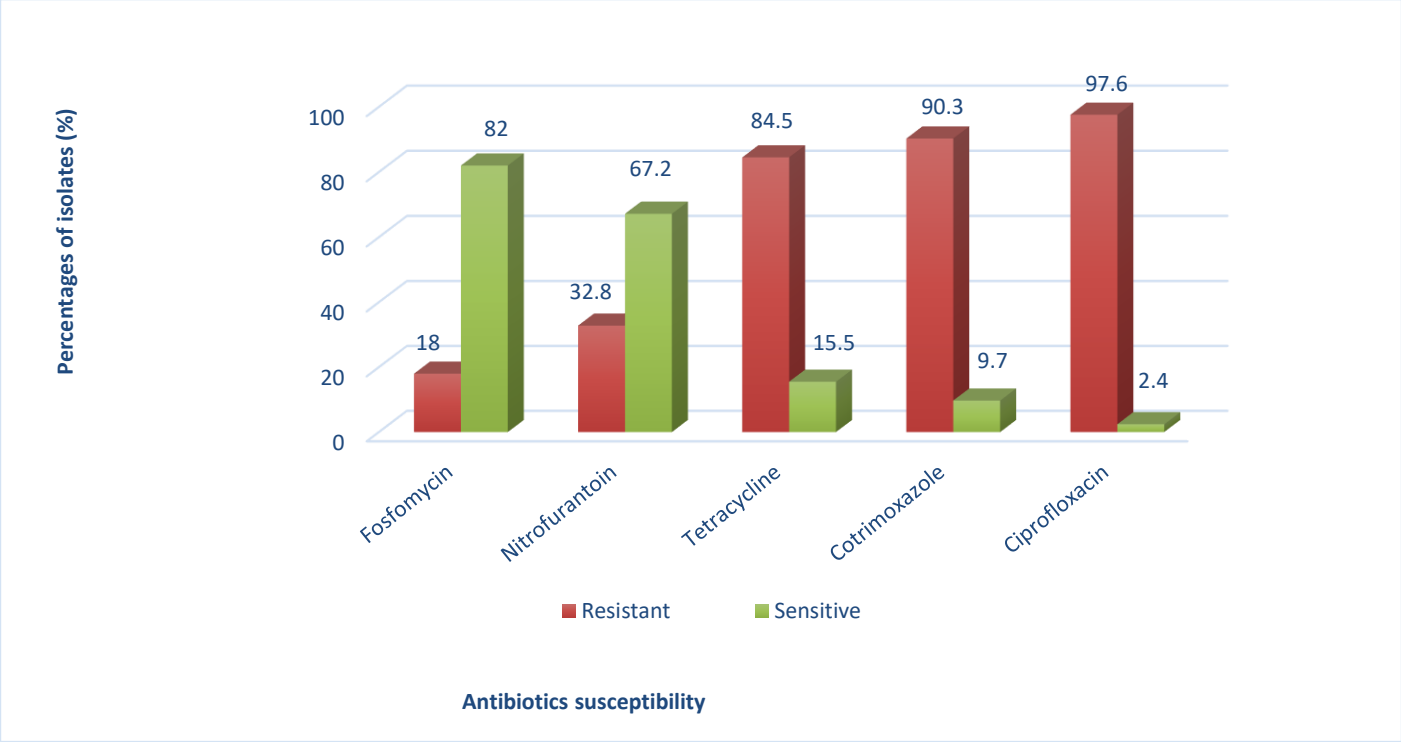

Figure-I: Susceptibility rates of oral antimicrobials against carbapenem-resistant *Escherichia coli* (n=978).

DISCUSSION

Around the world, *E. coli* is the most common cause of UTIs.[12] Recent years have seen an increase in carbapenem-resistant bacteria that cause UTIs in both hospital and community settings. This has created new and challenging obstacles for treatment decision-makers. Evolution of carbapenem resistance among Enterobacterales is posing a continuous burden on the healthcare settings due to limited treatment options.[6, 13]

The fact that carbapenem-resistant organisms frequently exhibit co-resistance to antibiotics exacerbates the already complex situation. Co-resistance in carbapenem-resistant gram-negative bacteria refers to the simultaneous resistance to multiple classes of antibiotics, apart from carbapenems. This phenomenon poses a significant challenge in the treatment of infections caused by these bacteria, as it limits the effectiveness of various antibiotic options and can lead to the use of last-resort antibiotics, further contributing to the development of antibiotic resistance.[14]

Infections caused by carbapenem-resistant Enterobacterales is associated with high morbidity and mortality among hospitalized patients. Carbapenem-resistant Enterobacterales contribute to a higher mortality rate among patients with complicated UTIs and urosepsis when compared to carbapenem-sensitive Enterobacterales.[15] Therefore, it is important and challenging to choose an appropriate empirical therapy especially in elderly patients with comorbidities.[12]

According to the present study, carbapenem-resistant *E. coli* showed the highest susceptibility to fosfomycin (82%). A study conducted in London also showed high susceptibility rates (60.5%) of fosfomycin against carbapenem-resistant Enterobacterales and 100% susceptibility against carbapenem-resistant *E. coli* isolates.[16] Additionally, according to various previous studies, over 90% of ESBL-producing *E. coli* isolates have shown susceptibility to fosfomycin. [17-20]

The present-day analysis found that 67.2% of carbapenem-resistant *E. coli* isolates were susceptible to nitrofurantoin. This finding is also consistent with various previous studies where >90% of ESBL-producing *E. coli* isolates demonstrated susceptibility to nitrofurantoin (17, 19, 20). However, another study found that nitrofurantoin inhibited only <25% of the carbapenem-resistant Enterobacterales.[16]

According to the present study, only 9.7% of carbapenem-resistant *E. coli* isolates demonstrated susceptibility to co-trimoxazole. This rate is significantly lower compared to rates reported other studies. For instance, one study found that 37.9% of ESBL producing *E. coli* isolates were susceptible to co-trimoxazole.[19] However, another study conducted in Japan found that 89% of Enterobacterales causing community-acquired UTIs were susceptible to co-trimoxazole.[21]

The current review found that only 2.4% of carbapenem-resistant *E. coli* isolates demonstrated susceptibility to ciprofloxacin. A study conducted in London also found that fewer than 25% of carbapenem-resistant Enterobacterales were susceptible to ciprofloxacin.[16] Similarly, another study conducted in Ethiopia found that only 20% of carbapenemase producing Enterobacterales were resistant to ciprofloxacin.[22]

The current study shows that nitrofurantoin and fosfomycin are effective in vitro against carbapenem-resistant *E. coli*. According to both the Infectious Diseases Society of America (IDSA) 2023 guidelines as well as the Sanford guide to antimicrobial therapy, nitrofurantoin and co-trimoxazole are the preferred antibiotics, whereas, fosfomycin is the alternative choice for treating uncomplicated cystitis.[23,24]

Considering the results of the present investigation, we recommend that fosfomycin and nitrofurantoin may be considered as empirical antibiotic choices for patients at risk of developing UTIs caused by carbapenem-resistant Enterobacterales, pending confirmation through culture results.

It is also important to note that the susceptibility rates of these antibiotics may vary between hospitals and their specific settings. Additionally, in light of the rising resistance rates, it is imperative to conduct continuous surveillance studies and generate site-specific antibiograms.

There are several limitations of the current study. It is a single-centred study. Further molecular analysis to identify the carbapenemases produced by the carbapenem-resistant *E. coli* isolates was not carried out due to budget constraints. Furthermore, the clinical response of patients on oral antimicrobials was not monitored as a part of this study.

CONCLUSION

The current study concluded that majority of carbapenem-resistant *E. coli* isolates causing urinary tract infections were susceptible to fosfomycin, followed by nitrofurantoin. Increased susceptibility to nitrofurantoin and fosfomycin suggests their potential utility as empirical treatments for urinary tract infections caused by carbapenem-resistant *E. coli*.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Nasrullah Malik: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, final approval of the version to be published

Aqib Sultan: Acquisition, analysis and interpretation of data and Drafting the work or revising it critically for important intellectual content and bench work.

Summiya Nizamuddin: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, final approval of the version to be published

Farah Shameem: Acquisition, analysis and interpretation of data

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