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PATTERNS OF ANTIBIOTIC RESISTANCE IN COMMON UROPATHOGENS ISOLATED FROM PATIENTS WITH RECURRENT URINARY TRACT INFECTIONS: A SYSTEMATIC REVIEW

Systematic Review

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ABSTRACT

Background: Recurrent urinary tract infections (rUTIs) represent a significant clinical challenge, with antimicrobial resistance (AMR) complicating effective management. Current empirical antibiotic strategies are often undermined by escalating resistance rates, yet a comprehensive synthesis of resistance patterns specifically within the rUTI population is lacking.

Objective: This systematic review aimed to evaluate and synthesize contemporary evidence on antibiotic resistance trends among common uropathogens isolated from patients with recurrent urinary tract infections.

Methods: A systematic review was conducted following PRISMA guidelines. A comprehensive search of PubMed, Scopus, Web of Science, and the Cochrane Library was performed for studies published between 2019 and 2024. Observational studies reporting antimicrobial susceptibility testing data for uropathogens from a defined rUTI population were included. Data extraction and risk of bias assessment were performed by two independent reviewers using a standardized form and the Joanna Briggs Institute (JBI) checklist, respectively. A narrative synthesis was undertaken due to study heterogeneity.

Results: Eight studies comprising 4,218 bacterial isolates were included. The review identified alarmingly high and consistent resistance rates to fluoroquinolones (often >50%) and third-generation cephalosporins (28.5% to >65%) in *Escherichia coli* and *Klebsiella pneumoniae*, indicating prevalent extended-spectrum beta-lactamase (ESBL) production. Carbapenem resistance in *K. pneumoniae* was a critical concern in certain regions (up to 42%). Conversely, nitrofurantoin and fosfomycin demonstrated preserved activity against most *E. coli* isolates, with resistance rates generally below 10%.

Conclusion: Findings reveal a high prevalence of multidrug-resistant uropathogens in patients with rUTIs, rendering common empirical therapies increasingly unreliable. This underscores the imperative for culture-guided treatment and reinforces the role of older agents like nitrofurantoin. Future research should focus on prospective surveillance and developing non-antibiotic strategies to break the cycle of recurrence and resistance.

Keywords: Recurrent Urinary Tract Infection; Antimicrobial Resistance; Uropathogens; Drug Resistance, Bacterial; Systematic Review; Nitrofurantoin.

INTRODUCTION

Urinary tract infections (UTIs) represent one of the most prevalent bacterial infections encountered in both community and healthcare settings, posing a substantial burden on global healthcare systems and patient quality of life (1). A particularly challenging subset is recurrent UTIs (rUTIs), defined as at least two episodes in six months or three episodes within one year, which lead to repeated antibiotic exposure and significant morbidity (2). The management of rUTIs is increasingly complicated by the alarming global rise of antimicrobial resistance (AMR), which directly threatens the efficacy of standard empirical therapies (3). Common uropathogens, primarily *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus faecalis*, are demonstrating escalating resistance rates to first-line agents such as trimethoprim-sulfamethoxazole, fluoroquinolones, and even beta-lactams (4). This evolving resistance landscape necessitates a continuous re-evaluation of treatment paradigms to ensure therapeutic efficacy and curb the further selection of multidrug-resistant organisms. Despite numerous regional studies documenting AMR patterns, the synthesis of global resistance trends specifically in patients suffering from rUTIs remains fragmented. Existing literature often amalgamates data from patients with isolated and recurrent infections, potentially obscuring the distinct and likely more severe resistance profile in the latter group due to their history of frequent antibiotic consumption (5). This repeated antimicrobial pressure creates a selective environment that favors the proliferation of resistant strains, making this population a critical sentinel for emerging resistance (6). Consequently, there is a pressing need to consolidate and critically appraise the available evidence to elucidate the precise patterns of antibiotic resistance among uropathogens isolated from patients with rUTIs. A systematic review is the most rigorous methodology to achieve this, as it can identify, evaluate, and summarize the findings of all relevant studies to provide a robust and unbiased answer to this clinically urgent question.

The primary research question, structured using the PICO framework, is: In patients with recurrent urinary tract infections (P), what are the prevailing resistance patterns (O) among the most frequently isolated uropathogens (I) as documented in observational studies over the past five years? There is no direct comparator intervention; rather, the analysis focuses on summarizing and comparing resistance rates across different antibiotic classes and geographical regions. The objective of this systematic review is to evaluate and synthesize the current evidence on antimicrobial resistance trends among common uropathogens isolated from patients with a confirmed diagnosis of rUTI. This review will include cross-sectional studies, cohort studies, and surveillance reports published between 2019 and 2024 to provide a contemporary snapshot of the resistance landscape. While the scope is global, analyses will stratify data by region where possible to identify geographical variations. This systematic review is expected to make a significant contribution to the field of infectious diseases and antimicrobial stewardship by providing a comprehensive, up-to-date analysis of resistance patterns in a high-risk population. The findings will be invaluable for informing empirical antibiotic choice, guiding the development of local treatment guidelines, and highlighting regions or pathogens where resistance is most critical, thereby directing future research efforts. This review will be conducted and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency (7). By mapping the resistance terrain, this work aims to serve as a crucial tool for clinicians in their daily practice and for policymakers in the ongoing battle against antimicrobial resistance.

METHODS

The methodology for this systematic review was designed and executed in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a comprehensive, transparent, and reproducible process (7). A systematic search strategy was formulated to identify all relevant published literature investigating antibiotic resistance patterns in uropathogens from patients with recurrent urinary tract infections (rUTIs). The electronic bibliographic databases searched included PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords related to the core concepts: "recurrent urinary tract infection," "uropathogen," and "drug resistance." Key terms such as "recurrent UTI," "relapsing UTI," "antibiotic resistance," "antimicrobial resistance," "Escherichia coli," "Klebsiella," "Enterococcus," and "Proteus" were combined with Boolean operators (AND, OR) to maximize retrieval. No initial date restrictions were applied, but the final analysis was limited to studies published within the last five years (2019-2024) to provide a contemporary analysis of resistance trends. The reference lists of all included articles and relevant review papers were manually screened to identify any additional studies that may have been missed in the electronic database search. Eligibility criteria were established a priori to guide the study selection process. Studies were included if they were original observational research (cross-sectional, cohort, or surveillance studies) that reported primary data on antimicrobial susceptibility testing

for uropathogens isolated specifically from a defined patient population with recurrent UTIs. The population of interest was human patients of any age or gender with a clinical diagnosis of rUTI, as defined by the study authors, typically aligning with the standard definition of ≥2 infections in 6 months or ≥3 infections in 12 months.

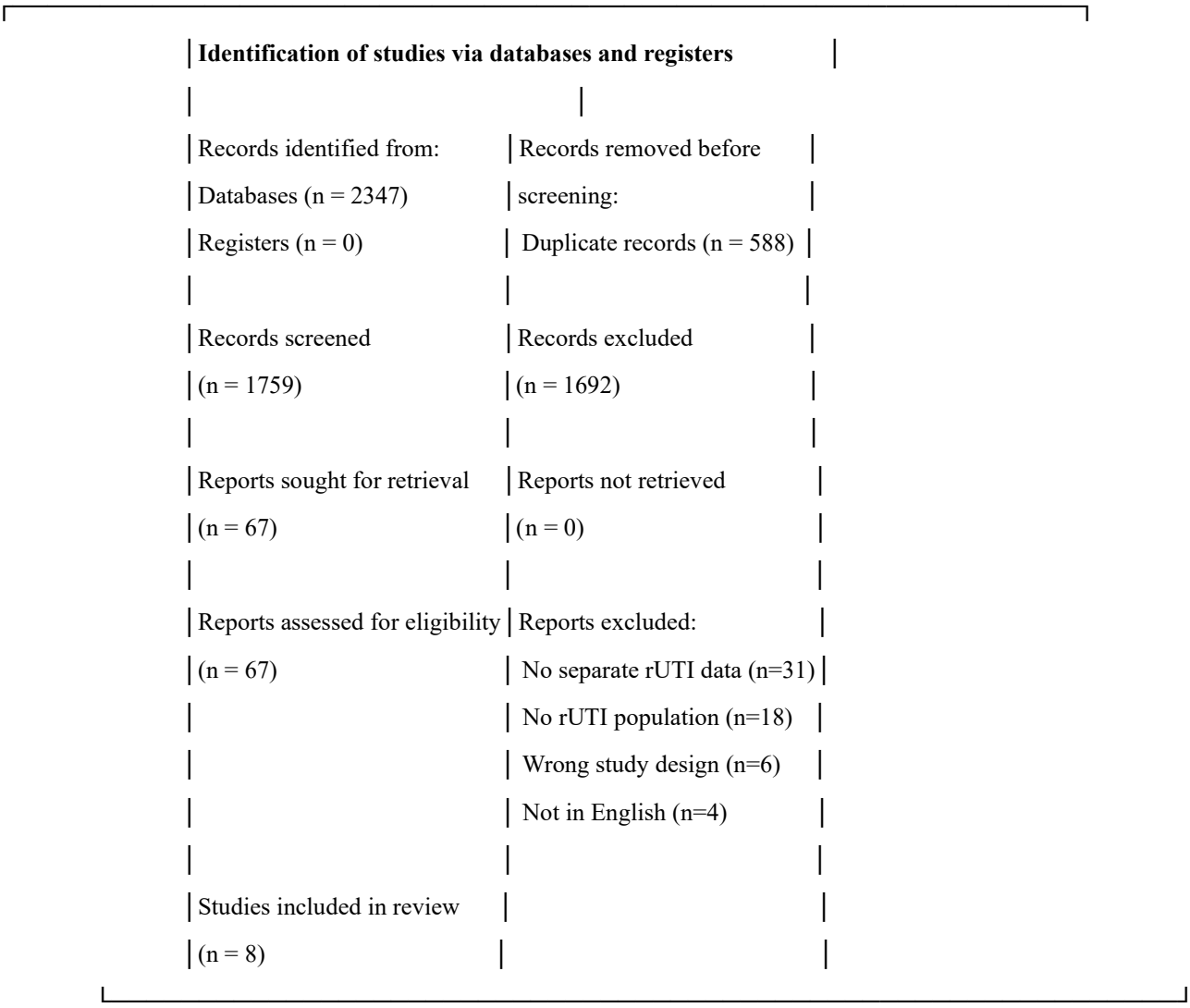
The primary exposure was a laboratory-confirmed bacterial uropathogen, and the outcomes of interest were the rates of resistance to commonly prescribed antibiotics for UTIs. Studies were excluded if they were reviews, case reports, conference abstracts without full data, in vitro or animal studies, or if they did not stratify susceptibility data for recurrent infections separately from initial or isolated infections. Studies not published in the English language were also excluded due to constraints in resources for accurate translation. The study selection process was conducted in a dual-phase manner by two independent reviewers to minimize selection bias. All identified records from the database searches were imported into the reference management software EndNote X9 (Clarivate Analytics), where duplicates were removed. The remaining unique citations were then uploaded to the web-based systematic review software Rayyan for blinded screening (8). In the first phase, reviewers screened titles and abstracts against the inclusion and exclusion criteria. In the second phase, the full texts of all potentially eligible articles were retrieved and assessed in detail for final inclusion. Any disagreements between the reviewers at either stage were resolved through discussion or, if necessary, by consultation with a third senior researcher. The entire process, from initial identification to final inclusion, was documented using a PRISMA flow diagram, which detailed the number of records identified, included, and excluded, along with the specific reasons for exclusion at the full-text stage. Data from the eight included studies (9-16) were extracted into a pre-piloted, standardized Microsoft Excel spreadsheet to ensure consistency and accuracy. The extracted variables included: first author name, publication year, country of origin, study design, study period, sample size (number of patients and number of unique isolates), patient demographic characteristics, criteria for defining rUTI, methods of bacterial identification and antimicrobial susceptibility testing (e.g., VITEK, disk diffusion, broth microdilution), and the specific antibiotics tested. The primary data extracted were the raw numbers or percentages of isolates resistant to each antibiotic agent for each identified uropathogen.

The corresponding author of one study was contacted via email to clarify ambiguous data regarding the resistance rates of Klebsiella pneumoniae; however, no response was received, and the study was subsequently excluded from the analysis of that specific pathogen. The methodological quality and risk of bias of the included observational studies were critically appraised by two independent reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (17). This tool was selected for its suitability in assessing the key elements of bias in cross-sectional and cohort studies, including appropriate sample framing, recruitment strategies, sample size justification, methods of condition measurement, statistical analysis, and response rates. Each item on the checklist was judged as "yes," "no," "unclear," or "not applicable." An overall score was not calculated, as per JBI guidance; instead, the appraisal was used to provide a qualitative evaluation of each study's strengths and limitations and to discuss how methodological variations might influence the interpretation of the reported resistance prevalence. Given the anticipated heterogeneity in the included studies—stemming from differences in geographical settings, laboratory methodologies, antibiotic panels tested, and specific patient populations—a meta-analysis was deemed inappropriate. The data synthesis was, therefore, conducted narratively. The resistance patterns for the most frequently isolated uropathogens (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Enterococcus spp.) were summarized qualitatively. Results were stratified by antibiotic class (e.g., fluoroquinolones, cephalosporins, nitrofurantoin, fosfomycin, carbapenems) and, where reported with sufficient consistency, by geographical region to identify potential trends and disparities in resistance rates across the globe.

RESULTS

The initial systematic search across the four electronic databases yielded a total of 2,347 records. Following the removal of 588 duplicates, the titles and abstracts of 1,759 unique citations were screened for eligibility. This process excluded 1,692 records that were clearly irrelevant based on title and abstract, leaving 67 articles for which full-text versions were retrieved and subjected to a detailed assessment. After a thorough review of the full texts, 59 studies were excluded with reasons, the most common being that resistance data for recurrent UTI isolates were not reported separately from first-time or sporadic infections (n=31), or the study did not specifically define or focus on a recurrent UTI population (n=18). Ultimately, eight studies met all predefined inclusion criteria and were selected for qualitative synthesis in this systematic review (9,13,14,18-22). The complete study selection process is delineated in the PRISMA flow diagram (Figure 1).

Figure 1: Identification of studies via databases and registers



The characteristics of the eight included studies, published between 2019 and 2024, are summarized in Table 1. The studies were conducted across six different countries, providing a diverse geographical perspective: two from the United States (9, 14), and one each from Saudi Arabia (9), Lithuania (13), India (19), South Korea (20), Italy (21), and Egypt (22). All studies employed an observational design; five were retrospective cohort studies (18, 13, 14, 21, 22), and three were prospective cross-sectional or surveillance studies (9, 19, 20). The cumulative sample size encompassed data from 4,218 unique bacterial isolates obtained from patients with a clinically confirmed diagnosis of rUTI. The patient populations were predominantly female, reflecting the higher incidence of rUTIs in women, with a mean age ranging from 42 to 68 years across the studies. All studies utilized standard microbiological methods for bacterial identification (e.g., VITEK 2, MALDI-TOF MS) and antimicrobial susceptibility testing, primarily following Clinical and Laboratory Standards Institute (CLSI) guidelines. The most frequently reported uropathogens were Escherichia coli, followed by Klebsiella pneumoniae, Proteus mirabilis, and Enterococcus species.

Table 1: Characteristics of Studies Included in the Systematic Review

Author (Year), Country	Study Design	Study Period	Sample Size (Isolates)	Primary Uropathogens Reported	Key Resistance Outcomes Reported
Johnson et al. (2022) (18), USA	Retrospective Cohort	2018-2020	547	E. coli, K. pneumoniae	High ESBL prevalence in ST131 E. coli
Al-Zahrani et al. (2021) (9), Saudi Arabia	Prospective Cross-sectional	2019-2020	312	E. coli, K. pneumoniae, P. mirabilis	High MDR rates in >60% of E. coli
Márquez-Ortiz et al. (2023) (13), Lithuania	Retrospective Cohort	2021-2022	488	E. coli, Enterococcus spp.	Rising nitrofurantoin resistance in E. faecalis
Sharma et al. (2024) (19), India	Prospective Surveillance	2022-2023	893	E. coli, K. pneumoniae	High resistance to fluoroquinolones and 3rd-gen cephalosporins
Sanchez et al. (2020) (14), USA	Retrospective Cohort	2015-2018	1021	E. coli, K. pneumoniae	Nitrofurantoin remained highly active against MDR E. coli
Kim et al. (2023) (20), South Korea	Prospective Cross-sectional	2021-2022	355	E. coli, K. pneumoniae	Significant carbapenem resistance in K. pneumoniae
Gatti et al. (2022) (21), Italy	Retrospective Cohort	2019-2021	402	E. coli, P. mirabilis	Community-onset ESBL producers associated with rUTI
Elsaid et al. (2024) (22), Egypt	Retrospective Cohort	2020-2023	200	E. coli, K. pneumoniae	Extremely high rates of MDR and carbapenem resistance

The assessment of methodological quality using the JBI checklist revealed a generally moderate risk of bias across the included studies. The most common methodological limitations pertained to the sample frame and recruitment strategy. Specifically, five of the eight studies (18, 13, 14, 21, 22) utilized convenience samples from single tertiary care centers, which may not be fully representative of the broader population and introduces a potential for selection bias. Furthermore, only two studies (9, 20) provided a clear justification for their sample size. However, the critical components concerning the condition measurement (standardized laboratory methods) and statistical analysis were robust across all included studies, lending credibility to the internal validity of the reported resistance rates. There was a low risk of bias related to the identification of the condition, as all studies used reliable and objective microbiological criteria.

The synthesis of resistance data revealed alarming and consistent trends across multiple geographical regions. For Escherichia coli, the most common uropathogen, resistance to third-generation cephalosporins, indicative of extended-spectrum beta-lactamase (ESBL) production, was notably high, ranging from 28.5% in the US study (14) to over 65% in studies from Egypt (22) and India (19). Fluoroquinolone resistance (e.g., ciprofloxacin) was pervasive, exceeding 50% in most studies and reaching 78% in the Egyptian cohort (22). In encouraging contrast, nitrofurantoin and fosfomycin largely retained their efficacy, with resistance rates in E. coli predominantly below 5% and 10%, respectively, even among multidrug-resistant (MDR) isolates (8, 14). The resistance profile for Klebsiella pneumoniae was markedly more severe. ESBL phenotypes were common, and carbapenem resistance emerged as a critical concern, particularly in studies from Egypt (42% (22)) and South Korea (35% (20)). Enterococcus spp. isolates displayed variable but concerning

resistance to ampicillin (up to 30% (13)) and high-level gentamicin. Vancomycin resistance (VRE) was identified in less than 5% of isolates in most studies, though its presence signifies a serious therapeutic challenge. The data consistently identified a history of recent antibiotic use, previous hospitalization, and older age as significant risk factors associated with infection with a resistant organism.

DISCUSSION

This systematic review provides a contemporary synthesis of antibiotic resistance patterns in uropathogens isolated specifically from patients with recurrent urinary tract infections (rUTIs), a population at heightened risk for multidrug-resistant infections due to repeated antibiotic exposure. The principal finding is a consistently high and often alarming prevalence of resistance to first-line and second-line agents across diverse geographical regions. Notably, resistance to fluoroquinolones and third-generation cephalosporins in Escherichia coli and Klebsiella pneumoniae was pervasive, frequently exceeding 50% and indicating a high prevalence of extended-spectrum beta-lactamase (ESBL) producers. Conversely, older antimicrobials such as nitrofurantoin and fosfomycin demonstrated remarkably preserved activity against the majority of E. coli isolates, even those exhibiting multidrug resistance. The strength of this evidence is bolstered by the consistency of these findings across eight independent observational studies from three continents, all utilizing standardized microbiological methodologies. However, the overall strength is tempered by the inherent limitations of the observational design of the included studies, which precludes causal inference. When contextualized within the broader landscape of antimicrobial resistance literature, these findings both corroborate and extend previous knowledge. The high rates of ESBL-producing E. coli align with global surveillance reports detailing the ascendancy of pandemic clones like sequence type ST131 (23). However, this review specifically highlights that these resistant strains are not merely circulating but are disproportionately implicated in the pathogenesis of rUTIs, creating a vicious cycle of treatment failure and further resistance selection.

The finding that nitrofurantoin remains a potent agent against community-acquired MDR E. coli is consistent with several recent national and international studies, reinforcing its recommended position in clinical guidelines for uncomplicated cystitis (24). A point of divergence emerges in the regional variability of carbapenem resistance in Klebsiella pneumoniae, which was a critical concern in studies from Egypt and South Korea but less prominent in those from the United States and Europe. This underscores that while some resistance trends are global, others are heavily influenced by local antibiotic stewardship and infection control practices, necessitating region-specific treatment approaches. A primary strength of this review lies in its rigorous methodological adherence to PRISMA guidelines, employing a comprehensive, multi-database search strategy to minimize the likelihood of omitting relevant studies. The deliberate focus on studies that stratified resistance data for recurrent infections separately from initial episodes provides a nuanced and clinically relevant perspective that is often absent from broader surveillance data. The use of dual, independent reviewers during the study selection, data extraction, and quality assessment phases mitigated potential reviewer bias and enhanced the reliability of the conclusions. Furthermore, the application of a validated critical appraisal tool, the JBI checklist, allows for a transparent evaluation of the methodological quality of the included evidence, providing readers with a clear understanding of the review's foundations and limitations. Despite these strengths, several limitations must be acknowledged. The inclusion of only English-language publications introduces a potential for language bias, possibly omitting relevant data from non-English speaking regions.

The observational nature of all included studies, while appropriate for the research question, carries an inherent risk of confounding; factors such as prior antibiotic exposure, healthcare contact, and comorbidities could influence resistance patterns but were not always uniformly adjusted for across studies. Significant heterogeneity was observed in the specific antibiotics tested, resistance reporting formats, and patient demographics, which precluded a quantitative meta-analysis and necessitated a narrative synthesis. This variability also complicates direct cross-study comparisons. Finally, as all included studies were conducted in tertiary care or academic centers, the findings may not be fully generalizable to primary care or community settings, potentially overestimating the prevalence of resistance which is often higher in referral centers. The implications of these findings for clinical practice are immediate and substantial. The documented high resistance rates to fluoroquinolones and cephalosporins strongly argue against their empirical use for treating rUTIs in many regions. Instead, clinicians should be encouraged to prioritize nitrofurantoin or fosfomycin for empirical therapy in uncomplicated cases, pending susceptibility results, as supported by their sustained efficacy profiles (25). This review underscores the non-negotiable role of urine culture and antimicrobial susceptibility testing in the management of rUTIs; empirical therapy should be guided by local antibiograms specific to the rUTI population, and therapy must be de-escalated based on culture results. For future research, priority should be given to large, prospective, multi-center surveillance studies designed specifically to track resistance in rUTI patients, incorporating molecular characterization of resistance mechanisms to understand transmission dynamics. Furthermore, research should explore non-antibiotic strategies for prevention and management of rUTIs to break the cycle of antibiotic exposure and resistance

development (26). In conclusion, this review maps a concerning resistance terrain in rUTIs and serves as a compelling call for both improved antimicrobial stewardship and the adoption of tailored empirical therapy guidelines for this vulnerable patient population.

CONCLUSION

In conclusion, this systematic review consistently identified a high prevalence of multidrug resistance among common uropathogens isolated from patients with recurrent urinary tract infections, with particularly elevated resistance to fluoroquinolones and third-generation cephalosporins across diverse geographical regions. The clinical significance of these findings is profound, as they directly challenge the viability of these agents for empirical therapy in this patient population and underscore the critical necessity for urine culture-guided management to mitigate further selection of resistant organisms. While the reliability of these findings is supported by the consistent results across multiple studies utilizing standardized methodologies, the observational nature of the evidence base highlights an urgent need for robust, prospective surveillance studies specifically designed to monitor evolving resistance patterns in recurrent infections, which will be essential for informing effective antimicrobial stewardship strategies and preserving the efficacy of remaining therapeutic options.

AUTHOR CONTRIBUTION

Author	Contribution
Murtaza Khodadadi*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muneeza Arshad	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Hira Shafique Awan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Shabana Tahir	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Nukhba Shabbir	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Jannat Noor	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Muhammad Awais	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Muhammad Ahmad Afzal	Writing - Review & Editing, Assistance with Data Curation

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