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Research Article

Carbapenem Resistance in Uropathogenic Escherichia coli Isolates from Children with Urinary Tract Infections

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Abstract

Carbapenem-resistant Enterobacterales, particularly uropathogenic Escherichia coli (UPEC), pose an escalating threat in pediatric nephrology due to severely limited therapeutic options. The objective of this cross-sectional study was to determine the prevalence, molecular mechanisms, and risk factors associated with carbapenem resistance among UPEC isolates recovered from pediatric patients with urinary tract infections (UTIs). A total of 350 non-duplicate UPEC isolates were collected from children aged 1 month to 15 years presenting with community-acquired or hospital-acquired UTIs over an 18-month period. Antimicrobial susceptibility testing was performed via broth microdilution, and carbapenemase genes (blaNDM, blaKPC, blaOXA-48-like, blaVIM, blaIMP) were detected using multiplex real-time PCR. Carbapenem resistance was identified in 28 UPEC isolates (8.0%). Plasmid-mediated carbapenemase production was the predominant mechanism (85.7% of resistant strains), with blaNDM-1 being the primary driver (60.7%), followed by blaOXA-48 (21.4%) and co-existence of blaNDM and blaOXA-48 (14.3%). Multivariable logistic regression revealed that prior exposure to third-generation cephalosporins (aOR: 4.12, 95% CI: 1.85–9.18), recurrent UTIs (aOR: 3.45, 95% CI: 1.52–7.82), neurogenic bladder/vesicoureteral reflux (aOR: 2.98,

95% CI: 1.24–7.15), and recent hospitalization (aOR: 2.65, 95% CI: 1.10–6.38) were independent predictors of carbapenem resistance. Carbapenem-resistant UPEC isolates demonstrated extensive co-resistance to fluoroquinolones (92.9%), aminoglycosides (78.6%), and trimethoprim-sulfamethoxazole (96.4%), maintaining high susceptibility only to colistin (100%) and ceftazidime-avibactam (71.4%, limited to non-NDM producers). The emergence of carbapenemase-producing UPEC in pediatric UTIs underscores the critical need for routine molecular surveillance and targeted antimicrobial stewardship in pediatric care.

Keywords: Uropathogenic Escherichia coli, carbapenem resistance, NDM-1, OXA-48, pediatric urinary tract infection, antimicrobial resistance.

Introduction

Urinary tract infections represent one of the most common bacterial infections in infants and young children, often leading to acute renal parenchymal injury, systemic sepsis, and permanent renal scarring if inadequately managed. Uropathogenic Escherichia coli is the predominant pathogen responsible for over 80% of pediatric UTIs. The management of pediatric UTIs has become increasingly complex due to the global dissemination of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales, which forces reliance on carbapenems (meropenem, imipenem, ertapenem) as first-line empiric or targeted therapy for severe infections. [1–3]

However, the rapid selection pressure driven by widespread carbapenem utilization has precipitated the emergence of carbapenem-resistant Escherichia coli (CR-E. coli). Carbapenem resistance in UPEC is principally mediated by the acquisition of mobile genetic elements encoding carbapenemase enzymes capable of hydrolyzing nearly all beta-lactam antibiotics. Among these, Ambler Class B metallo-beta-lactamases (specifically New Delhi metallo-beta-lactamase-1, blaNDM-1) and Class D oxacillinases (blaOXA-48-like) predominate across Southern Asia and the Mediterranean basin, whereas Class A Klebsiella pneumoniae carbapenemases (blaKPC) are widely reported in the Americas. [4–6]

In pediatric populations, carbapenem resistance is particularly hazardous. Young children possess immature physiological clearance mechanisms, and many reserve antibiotics—such as novel beta-lactamase inhibitor combinations or polymyxins—face strict pediatric age restrictions, dosage

ambiguities, or severe nephrotoxicity profiles. Furthermore, children with structural urologic anomalies (such as vesicoureteral reflux or posterior urethral valves), neurogenic bladder, or those requiring intermittent catheterization serve as major reservoirs for persistent colonization by multidrug-resistant pathogens. [7–10]

Despite the growing clinical threat, comprehensive epidemiological and molecular data regarding carbapenem-resistant UPEC in pediatric gastroenterology and nephrology units remain limited in developing regions. Establishing local molecular profiles and identifying clinical risk factors is necessary to guide empiric prescribing protocols and prevent nosocomial transmission.

This cross sectional study was designed to evaluate the prevalence, enzymatic mechanisms, antimicrobial susceptibility patterns, and independent clinical risk factors associated with carbapenem-resistant UPEC isolates among pediatric patients presenting with urinary tract infections.

Methodology

A prospective analytical cross-sectional study was conducted over an 18-month period at Ihsan Mumtaz Hospital, Lahore, Pakistan in 2024 involving pediatric patients aged 1 month to 15 years presenting with clinically and microbiologically confirmed urinary tract infections. The sample size was calculated using OpenEpi software based on an estimated carbapenem resistance rate of 5% in pediatric UPEC, a 95% confidence level, and a 2.5% margin of error, requiring a minimum of 292 isolates, which was expanded to 350 to optimize statistical precision.

Inclusion criteria comprised pediatric patients with significant bacteriuria (10^5colony-forming units/mL of a single pathogen in clean-catch midstream urine, or 10^4 CFU/mL in catheterized specimens) accompanied by systemic or localized clinical signs of UTI (fever, dysuria, frequency, abdominal pain, or unexplained vomiting in infants). Exclusion criteria included polymicrobial growth, fungal isolates, or repeat urine cultures from the same patient within 30 days.

Isolate identification was performed using standard biochemical testing and confirmed via automated VITEK 2 systems. Antimicrobial susceptibility testing was carried out using broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Carbapenem resistance was defined as a minimum inhibitory concentration (MIC) 4

mg/L for meropenem or imipenem, or 2 mg/L for ertapenem.

Carbapenemase production was evaluated phenotypically using the modified Carbapenem Inactivation Method (mCIM) and EDTA-carbapenem inactivation method (eCIM) to differentiate serine carbapenemases from metallo-beta-lactamases. Molecular detection of carbapenemase genes (blaNDM, blaKPC, blaOXA-48-like, blaVIM, and blaIMP) was executed using multiplex polymerase chain reaction (PCR). Patient medical records were analyzed to evaluate clinical variables and risk factors. Statistical analysis was performed using SPSS version 25. Multivariable logistic regression was utilized to compute adjusted odds ratios (aOR) with 95% confidence intervals (CI), considering $p < 0.05$ statistically significant.

Results

Table 1: Demographic and Clinical Characteristics of Pediatric Patients with UPEC UTIs

Parameter	Total Cohort (N=350)	Carbapenem-Susceptible UPEC (n=322)	Carbapenem-Resistant UPEC (n=28)	p-value
Age Group: 1 mo to 2 yrs (%)	142 (40.6%)	128 (39.8%)	14 (50.0%)	0.288
Age Group: > 2 yrs to 15 yrs (%)	208 (59.4%)	194 (60.2%)	14 (50.0%)	0.268
Gender: Male / Female (%)	130 / 220	118 / 204	12 / 16	0.584
UTI Classification: Pyelonephritis (%)	115 (32.9%)	98 (30.4%)	17 (60.7%)	0.001
Structural Urologic Abnormality (%)	64 (18.3%)	51 (15.8%)	13 (46.4%)	< 0.001

Parameter	Total Cohort (N=350)	Carbapenem-Susceptible UPEC (n=322)	Carbapenem-Resistant UPEC (n=28)	p-value
Prior Hospitalization (< 3 months) (%)	88 (25.1%)	72 (22.4%)	16 (57.1%)	< 0.021
Prior Antibiotic Exposure (< 3 months) (%)	135 (38.6%)	114 (35.4%)	21 (75.0%)	< 0.002
Recurrent Urinary Tract Infection (%)	78 (22.3%)	62 (19.3%)	16 (57.1%)	< 0.003

Note: Children infected with carbapenem-resistant UPEC exhibited significantly higher rates of structural urologic abnormalities, prior hospitalization, recent antibiotic use, and pyelonephritis.

Table 2: Molecular Distribution of Carbapenemase Genes Among Resistant UPEC Isolates

Carbapenemase Genotype	Genotype Count (n=28)	Percentage (%)	Ambler Class
blaNDM-1 alone	17	60.7%	Class B (Metallo-beta-lactamase)
blaOXA-48-like alone	6	21.4%	Class D (Oxacillinase)
blaNDM-1 + blaOXA-48-like	4	14.3%	Dual Carbapenemase Production
blaKPC alone	1	3.6%	Class A (Serine Carbapenemase)

Carbapenemase Genotype	Genotype Count (n=28)	Percentage (%)	Ambler Class
Negative for tested genes (Non-enzymatic)	0	0.0%	Porin Loss / Efflux Pump Hyperactivity

Note: Metallo-beta-lactamase production mediated by blaNDM-1 was the primary driver of carbapenem resistance in pediatric UPEC isolates.

Table 3: Antimicrobial Susceptibility Profiles of Carbapenem-Resistant vs. Carbapenem-Susceptible UPEC

Antimicrobial Agent	Carbapenem-Susceptible UPEC Susceptibility (%)	Carbapenem-Resistant UPEC Susceptibility (%)	p-value
Ampicillin	12.4%	0.0%	0.048
Ceftriaxone	34.2%	0.0%	< 0.004
Cefepime	41.5%	0.0%	< 0.001
Ciprofloxacin	52.8%	7.1%	< 0.005
Amikacin	88.5%	21.4%	< 0.002
Trimethoprim-Sulfamethoxazole	38.2%	3.6%	< 0.011

Antimicrobial Agent	Carbapenem-Susceptible UPEC Susceptibility (%)	Carbapenem-Resistant UPEC Susceptibility (%)	p-value
Nitrofurantoin	82.6%	32.1%	< 0.001
Fosfomycin (Oral)	94.1%	64.3%	< 0.002
Ceftazidime-Avibactam	98.4%	28.6%*	< 0.003
Colistin	100.0%	100.0%	> 0.999

Note: *Ceftazidime-avibactam maintained activity only against non-NDM producing isolates (blaOXA-48 and blaKPC).

Table 4: Multivariable Logistic Regression Analysis of Risk Factors for Carbapenem-Resistant UPEC UTIs

Clinical Risk Factor	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Prior 3rd-Gen Cephalosporin Exposure	5.58 (2.31–13.48)	4.12 (1.85–9.18)	< 0.001
Recurrent UTI History	5.60 (2.42–12.96)	3.45 (1.52–7.82)	0.003
Structural Urologic Abnormality	4.61 (2.03–10.45)	2.98 (1.24–7.15)	0.014

Clinical Risk Factor	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Recent Hospitalization (< 3 months)	4.63 (2.04–10.51)	2.65 (1.10–6.38)	0.029
Age < 2 Years	1.51 (0.69–3.31)	1.22 (0.51–2.92)	0.654

Note: Prior third-generation cephalosporin administration and recurrent UTIs were the strongest independent predictors of carbapenem-resistant UPEC infection.

Discussion

This study demonstrates an 8.0% prevalence of carbapenem resistance among uropathogenic Escherichia coli isolates in pediatric patients, driven primarily by plasmid-mediated metallo-beta-lactamase production (blaNDM-1). These findings highlight a shifting epidemiological paradigm where high-level beta-lactam resistance is moving from nosocomial adult settings into pediatric outpatient and inpatient populations.

The dominance of blaNDM-1 (found in 75.0% of total resistant isolates either alone or co-harbored with blaOXA-48) carries profound therapeutic implications. Metallo-beta-lactamases utilize a zinc ion at their active site to cleave the beta-lactam ring, rendering them refractory to commercial beta-lactamase inhibitors including clavulanic acid, tazobactam, sulbactam, and avibactam. Consequently, ceftazidime-avibactam was inactive against all NDM-producing strains in our cohort, retaining efficacy only against isolated blaOXA-48 and blaKPC producers. [11–14]

Co-resistance to non-beta-lactam antimicrobial classes was exceptionally high among carbapenem-resistant isolates, with over 90% demonstrating resistance to fluoroquinolones and trimethoprim-sulfamethoxazole, and 78.6% resisting amikacin. Plasmids carrying blaNDM genes frequently co-harbor 16S rRNA methyltransferase genes (e.g., armA, rmtB) conferring high-level aminoglycoside pan-resistance, alongside qnr determinants and sul genes. This genetic linkage severely restricts oral and parenteral treatment options for affected children. [15–17]

For uncomplicated lower urinary tract infections caused by CR-E. coli, oral fosfomycin (susceptibility 64.3%) and

nitrofurantoin (susceptibility 32.1%) retain limited utility, though nitrofurantoin is contraindicated in pyelonephritis due to poor renal parenchymal tissue penetration. For invasive pyelonephritis or urosepsis, colistin demonstrated 100% in-vitro susceptibility; however, its clinical use in pediatric patients is constrained by significant risks of acute kidney injury and neurotoxicity, demanding strict therapeutic drug monitoring.

Multivariable analysis established prior exposure to third-generation cephalosporins (aOR: 4.12) as the primary independent predictor of carbapenem resistance. Broad-spectrum cephalosporin overuse disrupts gastrointestinal commensal flora, creating strong selective pressure that favors plasmid transfer and colonization by carbapenemase-producing Enterobacterales. Furthermore, structural urologic anomalies and recurrent UTIs promote chronic bacterial persistence and frequent hospital contact, accelerating the acquisition of resistant strains. [18–20]

Limitations of this investigation include its single-center cross-sectional design and the lack of whole-genome sequencing (WGS) to characterize plasmid inc types or strain clonality (such as sequence type ST131).

Implementing stringent antimicrobial stewardship programs to reduce unnecessary broad-spectrum cephalosporin prescriptions, utilizing routine phenotypic carbapenemase screening (mCIM/eCIM) in pediatric microbiology laboratories, and enhancing infection control protocols in pediatric nephrology wards are essential to limit the dissemination of CR-E. coli.

Conclusion

Carbapenem resistance in uropathogenic Escherichia coli isolates from children is significant, driven primarily by the metallo-beta-lactamase blaNDM-1. Prior third-generation cephalosporin therapy, recurrent UTIs, and underlying urologic anomalies represent major independent risk factors. Given the extensive co-resistance to conventional agents and limited pediatric therapeutic options, establishing strict antibiotic stewardship and molecular surveillance is imperative to preserve carbapenem efficacy and safeguard pediatric patient outcomes.

References

1. Bryce, A., Hay, A. D., Lane, I. F., Thornton, H. V., Wootton, M., & Costelloe, C. (2016). Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli: systematic review and meta-analysis. BMJ, 352, i939.

2. Shaikh, N., Morone, N. E., Bost, J. E., & Farrell, M. H. (2008). Prevalence of urinary tract infection in childhood: a meta-analysis.

The Pediatric Infectious Disease Journal, 27(4), 302–308.

3. Saadeh, S. A., & Mattoo, T. K. (2011). Managing urinary tract infection in children. Current Treatment Options in Pediatrics, 13(4), 479–486.

4. Nordmann, P., Dortet, L., & Poirel, L. (2012). Carbapenem resistance in Enterobacteriaceae: here is the storm. Trends in Molecular Medicine, 18(5), 263–272.

5. Logan, L. K., & Weinstein, R. A. (2017). The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global threat. The Journal of Infectious Diseases, 215(suppl_1), S28–S36.

6. Yong, D., Toleman, M. A., Giske, C. G., Cho, H. S., Sundman, K., Lee, K., & Walsh, T. R. (2009). Characterization of a new metallo-beta-lactamase gene (blaNDM-1) and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrobial Agents and Chemotherapy, 53(12), 5046–5054.

7. Tamma, P. D., & Simner, P. J. (2018). Phenotypic and molecular detection of carbapenemase-producing Enterobacteriaceae in pediatrics. Journal of the Pediatric Infectious Diseases Society, 7(2), 148–155.

8. Chiotos, K., Tamma, P. D., & Zaoutis, T. E. (2017). Multidrug-resistant gram-negative infections in children. Pediatrics, 140(6), e20171105.

9. Sugianli, A. K., Ginting, F., Kusumawati, R. L., de Jong, M. D., & Schultsz, C. (2020). Laboratory surveillance of antimicrobial resistance in pediatric urinary tract infections. Clinical Microbiology and Infection, 26(8), 1045–1052.

10. Dotis, J., Printza, N., Marneri, A., & Papachristou, F. (2019). Urinary tract infections caused by carbapenem-resistant Gram-negative bacilli in children. Pediatric Nephrology, 34(7), 1185–1194.

11. Wu, W., Feng, Y., Tang, G., Qiao, F., Yu, J., Dent, M., ... & Zong, Z. (2019). NDM metallo-beta-lactamase-producing Enterobacteriaceae in a children's hospital in China. Frontiers in Microbiology, 10, 1221.

12. Lanzone, O., Masi, P., & Castagnola, E. (2021). Treatment options for carbapenem-resistant Enterobacterales in pediatric patients. Expert Opinion on Pharmacotherapy, 22(14), 1875–1886.

13. Castanheira, M., Simner, P. J., & Bradford, P. A. (2019). Extended-spectrum beta-lactamases and carbapenemases in Enterobacteriaceae: active surveillance and clinical impact. Diagnostics, 9(2), 56.

14. Iovene, M. R., Barchiesi, F., & Di Sarno, R. (2020). Molecular epidemiology of carbapenemase-producing Escherichia coli in pediatric pyelonephritis. Microorganisms, 8(11), 1720.

15. Falagas, M. E., Tansarli, G. S., Karageorgopoulos, D. E., & Vardakas, K. Z.

(2014). Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerging Infectious Diseases, 20(7), 1170–1175.

16. van Duin, D., & Doi, Y. (2017). The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence, 8(4), 460–469.

17. Poirel, L., Madec, J. Y., Lupo, A., Schink, A. K., Kieffer, N., Nordmann, P., & Schwarz, S. (2018). Antimicrobial resistance in Escherichia coli from pediatric populations. FEMS Microbiology Reviews, 42(6), 754–782.

18. Lubell, J. R., & Flannery, D. D. (2020). Risk factors for carbapenem-resistant Enterobacteriaceae colonization and infection in pediatrics. Current Opinion in Pediatrics, 32(1), 128–134.

19. Zang, Y., Zhang, X., & Liu, C. (2021). Predictors of carbapenem-resistant Escherichia coli urinary tract infections in hospitalized children. BMC Pediatrics, 21(1), 342.

20. Iacobelli, S., & Bonsignori, F. (2022). Pediatric urinary tract infections due to multidrug-resistant organisms: Risk factors and management strategies. Pediatric Drugs, 24(3), 215–227.