

Letter to Editor

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Dual carbapenem-fluoroquinolone resistance in community-onset pediatric urinary tract infections: Phenotypic-genotypic integration in three cases

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Urinary tract infections (UTIs) are among the most prevalent pediatric bacterial infections, and undertreated episodes may lead to renal scarring, hypertension, or chronic kidney disease. Multidrug-resistant (MDR) Enterobacterales have been increasingly reported in children, with higher rates in Asian and Middle Eastern settings than in high-income countries[1,2]. What is still considered uncommon in pediatrics is concomitant carbapenem and fluoroquinolone resistance (CFR): even large 10-year pediatric series found carbapenem resistance in only 2.1%-2.9% of isolates, suggesting that the subgroup that is both carbapenem-resistant and fluoroquinolone-resistant is small but clinically important[3]. Current Infectious Diseases Society of America (IDSA) guidance recommends the use of molecular assays for antibiotic resistance genes to reconcile phenotype and genotype in MDR or complicated Gram-negative infections, but actual use in low- and middle-income countries is limited by cost and laboratory capacity[4,5].

We retrospectively identified three community-onset pediatric UTIs in Vietnam, all in children without classic healthcare-associated risk factors, caused by MDR Enterobacterales exhibiting dual carbapenem and fluoroquinolone resistance. Each case was successfully managed by integrating automated antimicrobial susceptibility testing with a targeted multiplex polymerase chain reaction (PCR) resistance panel. This phenotype-genotype integration supported stewardship-concordant decisions in all cases, aligning with recommendations for mechanism-directed therapy[4,6].

The first was a 15-month-old girl with one week of fever and dysuria despite amoxicillin-clavulanate therapy. A clean-catch urine specimen yielded *Escherichia* (*E.*) *coli* (>10^5 CFU/mL). Antimicrobial susceptibility testing revealed resistance to β-lactams, carbapenems, and fluoroquinolones, but susceptibility to aminoglycosides; multiplex PCR detected *bla*CIT, *bla*DHA, *mcr-1*, *bla*OXA-48, *bla*CTX-M9, *qnrB*, and *aac*(6′)-*Ib-cr*. Gentamicin (5 mg/kg/day×7 days) led to defervescence within 48 h and a sterile follow-up urine culture at day 30. No nephrotoxicity or ototoxicity occurred. Phenotype-genotype correlation was fully concordant.

The second case was a 5-year-old girl with 2 days of fever and dysuria, had *Proteus mirabilis* (>10^5 CFU/mL). Aantimicrobial susceptibility testing showed resistance to β-lactams, carbapenems, and levofloxacin, but susceptibility to ciprofloxacin and aminoglycosides. Multiplex PCR identified *bla*DHA, *bla*OXA-48, *bla*NDM-1, and *qnrB*. She received ciprofloxacin (30 mg/kg/day for 7 days) following failure of oral cefixime, with symptom resolution. This case demonstrated partial phenotype-genotype concordance, as fluoroquinolone findings were discordant (susceptibility to ciprofloxacin despite *qnrB* detection).

The third case was a 12-year-old boy with one month of urinary frequency without fever or dysuria following multiple outpatient antibiotic courses. Urine culture yielded *Klebsiella pneumoniae* (10^5 CFU/mL) with broad resistance on antimicrobial susceptibility testing and susceptibility only to levofloxacin; multiplex PCR detected no antibiotic resistance genes, resulting in marked

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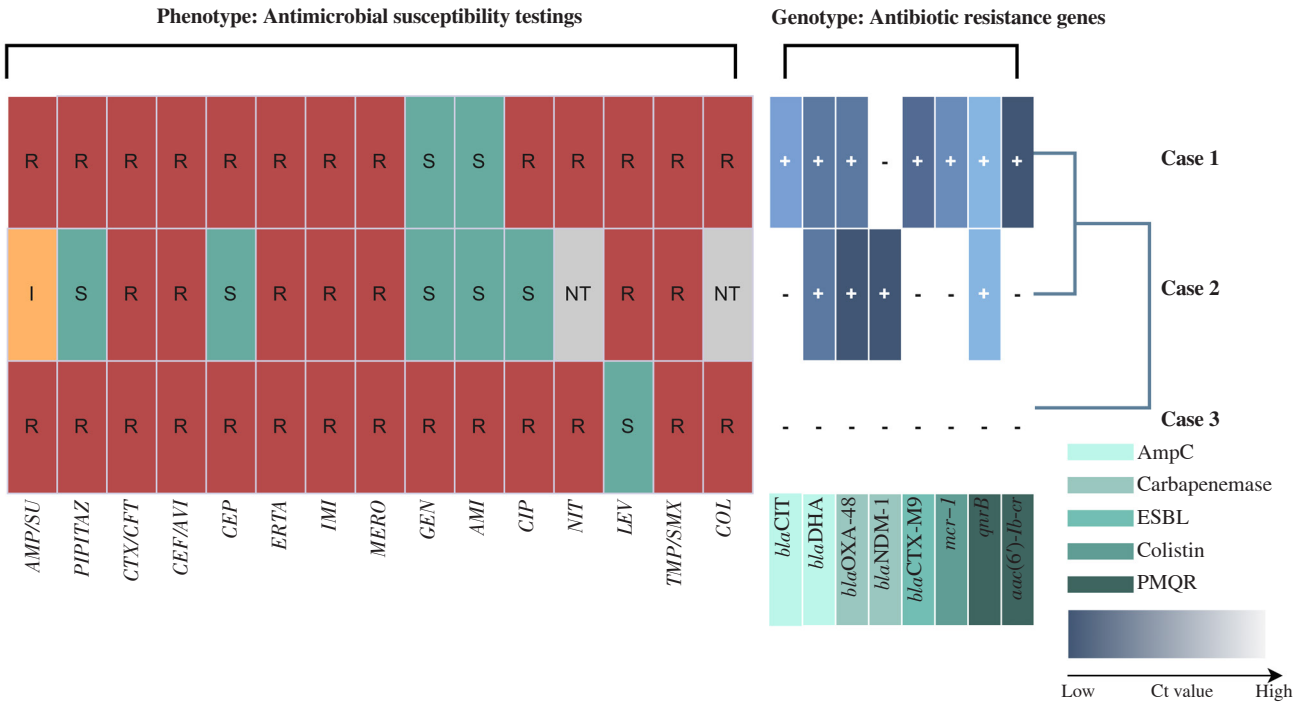

Figure 1. Phenotype and genotype in three pediatric MDR-UTI cases. Phenotype: AST by VITEK2 per CLSI M100, 35th edition. Genotype: multiplex polymerase chain reaction ARGs, shading by Ct (darker=higher load), white=not detected. Cases 1-2 share *bla*DHA, *bla*OXA-48, *qnrB*; Case 3 shows no ARGs. AST: antimicrobial susceptibility testing; ARGs: antibiotic resistance genes; MDR: multidrug-resistant; UTI: urinary tract infection; R: resistant; I: susceptible, increased exposure; S: susceptible; NT: not tested; AMP/SUL: ampicillin/sulbactam; PIP/TAZ: piperacillin/tazobactam; CTX/CFT: cefotaxim/ceftriaxone; CEF/AVI: ceftazidim/avibactam; CEP: cefepime; ERTA: ertapenem; IMI: imipenem; MERO: meropenem; GEN: gentamicin; AMI: amikacin; CIP: ciprofloxacin; NIT: nitrofurantoin; LEV: levofloxacin; TMP/SMX: trimethoprim/sulfamethoxazole; COL: colistin; CLSI: Clinical and Laboratory Standards Institute; Ct: cycle threshold.

phenotype-genotype discordance. Levofloxacin (10 mg/kg/day) was administered for 10 days, with clinical improvement noted only after day 10. He completed a total of 20 days of therapy and was asymptomatic with a sterile urine culture at one month follow-up.

Figure 1 shows phenotypic susceptibility profiles and multiplex PCR-detected resistance genes in the three pediatric MDR-UTI cases.

Mechanistically, plasmid-mediated AmpC β-lactamases (*bla*DHA/*bla*CIT) confer resistance to third-generation cephalosporins. Overexpression may impair cefepime activity, while avibactam more reliably restores activity than clavulanate or tazobactam[7]. Extended-spectrum β-lactamases (ESBLs; *bla*CTX-M9) hydrolyze oxyimino-cephalosporins and may compromise cefepime; guidelines recommend carbapenems for severe infections, with ceftazidime/avibactam as an option when metallo-β-lactamases are absent[4]. OXA-48-like carbapenemases (*bla*OXA-48) confer low-to-moderate carbapenem minimum inhibitory concentrations (MICs) with limited cephalosporin activity; consequently, ceftazidime/avibactam remains active in the absence of MBLs. In contrast, *bla*NDM-1 hydrolyzes nearly all β-lactams except aztreonam; thus, aztreonam/avibactam (or aztreonam plus ceftazidime/avibactam) is preferred if available[4]. Plasmid-mediated quinolone resistance, notably *aac*(6′)-*Ib-cr* (acetylates aminoglycosides and fluoroquinolones) and *qnrB* (protects gyrase/topoisomerase Ⅳ), modestly elevates fluoroquinolone MICs but facilitates *gyrA*/*parC* mutations, driving high-level resistance[8].

In Case 1, the *E. coli* urine isolate showed strong genotype-phenotype concordance. *bla*OXA-48 can drive carbapenem non-susceptibility in the absence of MBLs, typically *via* low-to-moderate MIC elevations amplified by porin loss and/or co-produced ESBL/AmpC enzymes. Despite *aac*(6′)-*Ib-cr* carriage, preserved gentamicin/amikacin susceptibility is plausible in the absence of *16S*-rRNA methylases or highly expressed aminoglycoside-modifying enzymes.

In Case 2, antimicrobial susceptibility testing showed a levofloxacin-resistant/ciprofloxacin-susceptible profile. *qnrB* carriage may modestly elevate MICs, leading to the confirmation of levofloxacin resistance *via* current CLSI breakpoints. By contrast, cefepime and piperacillin/tazobactam susceptibility is implausible

Table 1. Recommendations for integrated phenotypic-genotypic approach to antimicrobial stewardship from three cases.

Steps	When to use	Key actions	Output for clinicians	Stewardship note
1. Specimen and pre-analytics	Before antibiotics if feasible	Proper urine collection; quantitative culture	High-quality specimen and context	Prevents unnecessary therapy
2. Baseline phenotype	All culture-positive UTIs	Panel appropriate for pediatric UTIs	Initial AST profile; red-flag phenotypes	Anchors early de-escalation/ escalation
3. Targeted genotype	MDR/XDR; severe disease; high-risk phenotype	Detect ESBL; AmpC; PMQR; carbapenemases; AMEs; 16S methylases	Mechanism identified or excluded	Enables mechanism-directed choices; avoids unnecessary carbapenems
4. Reconcile phenotype-genotype	Discordance or unusual split	Concordant: proceed Step 5; Discordant: repeat Step 2/3; review breakpoints; consider off-panel genes; add targeted assays (if possible)	Actionable, clarified report with interpretive comment	Maintains accuracy and avoids over- or under-treatment
5. Mechanism-guided therapy	After mechanism and MIC known	Select narrowest active agent according to current recommendations	Tailored regimen	Carbapenem-sparing when safe/ possible
6. Follow-up	Clinical response and labs	Define duration by site/severity; monitor toxicity; education; selective test-of-cure	Safe completion	Sustains stewardship gains

UTIs: urinary tract infections; MDR: multidrug-resistant; XDR: extensively drug-resistant; ESBL: extended-spectrum β-lactamase; PMQR: plasmid-mediated quinolone resistance; AMEs: aminoglycoside-modifying enzymes; MIC: minimum inhibitory concentration.

with *bla*NDM-1/*bla*OXA-48 co-expression. IDSA guidelines caution against cephalosporins or β-lactam/β-lactamase inhibitor combinations for MBL producers, even when *in vitro* results suggest susceptibility, given high clinical failure rates.

Case 3 showed striking phenotype-genotype discordance: despite an extensively drug-resistant profile by antimicrobial susceptibility testing, no antibiotic resistance genes were detected. Likely explanations include off-panel resistance mechanisms, porin loss (*omp*K35/*omp*K36) with AcrAB-TolC efflux layered on ESBL/AmpC activity, undetected ESBL/AmpC variants or chromosomal hyperproduction, and aminoglycoside resistance from untested 16S-rRNA methylases/aminoglycoside-modifying enzymes. The levofloxacin-susceptible result implies minimal *gyrA*/*parC* mutations and low efflux activity.

These findings underscore the limitations of narrow mPCR panels and support broader genotyping or add-on assays when phenotype-genotype discordance is substantial, consistent with current integrated antimicrobial susceptibility testing frameworks[6].

Phenotype-genotype integration supported stewardship-concordant therapy in all three carbapenem and fluoroquinolone resistance cases[4,6]. In Case 1, full concordance with preserved aminoglycoside activity justified gentamicin use, aligning with pediatric series from Nepal (87%) and Turkey (99%) where *E. coli* often remains aminoglycoside-susceptible despite MDR[9]. In Case 2, carriage of *bla*OXA-48/*bla*NDM-1/*qnrB* with ciprofloxacin susceptibility allowed ciprofloxacin use while avoiding β-lactam/β-lactamase inhibitor combinations, which IDSA advises against for MBL producers. In Case 3, despite no antibiotic resistance genes being detected, antimicrobial susceptibility testing-confirmed levofloxacin susceptibility guided therapy, paralleling pediatric *Klebsiella* cohorts with 90%-93% levofloxacin susceptibility[10].

In many developing settings, access to newer agents is limited, with pediatric use further constrained by pharmacokinetic, dosing, and availability barriers. Yet even as MDR and rare dual carbapenem and fluoroquinolone resistance phenotypes emerge, IDSA guidance remains clinically applicable: it prioritizes organism- and mechanism-directed therapy, permitting fluoroquinolones or aminoglycosides when susceptibility is confirmed, while reserving advanced agents for complicated disease. Crucially, a phenotype-genotype reconciliation strategy enables stewardship-aligned decisions despite resource constraints. From these cases, we recommend an integrated phenotypic-genotypic approach to antimicrobial stewardship in complicated MDR-UTIs. The practical workflow is summarized in Table 1.

In summary, pediatric MDR-UTIs are increasing and occasionally exhibit dual carbapenem and fluoroquinolone resistance. Integrating rapid molecular diagnostics with standard antimicrobial susceptibility testing clarifies resistance mechanisms and enables tailored therapy. Early recognition and robust antimicrobial stewardship are essential to improve outcomes and curb transmission, paired with a clear hospital-level infection control strategy to prevent spread among children.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethics approval and consent to participate

Written informed consents were obtained from the patients' families for the publication of these case reports. Institutional approval for case publication was granted by the Department of Pediatric Cardiology and Nephrology, Can Tho Children's Hospital (Approval No. CV-BN03/TM/BVN CT/2025).

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Authors' contributions

QNC: Conceived and designed the study, curated and collected data, drafted the manuscript. HTD: Supervised the project, critically reviewed and revised the manuscript for important intellectual content. THT: Performed laboratory analyses, prepared the illustrative figure, reviewed and revised the manuscript. NNQ: Verified data accuracy, reviewed and revised the manuscript.MLH: Verified data accuracy, reviewed and revised the manuscript.

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