Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2015; 3(4C): 1818-1825 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com DOI: 10.36347/sjams.2015.v03i04.046

Research Article

Serum and Urinary Drug Concentration Monitoring of Antibiotics Used in Complicated Urinary Tract Infections: Implications for Therapeutic Drug Monitoring Protocols

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Abstract: ***Background:*** Complicated urinary tract infections (cUTIs) caused by multidrug-resistant (MDR) organisms represent a significant clinical challenge requiring precise pharmacokinetic (PK)/pharmacodynamic (PD) optimization. Inadequate drug concentrations at the site of infection contribute to therapeutic failure and resistance emergence. ***Objective:*** To quantify and compare serum and urinary drug concentrations of ciprofloxacin, piperacillin-tazobactam, and meropenem in hospitalized patients with cUTIs and to delineate their implications for Therapeutic Drug Monitoring (TDM) protocols. ***Methods:*** A prospective observational study was conducted across two tertiary care centers in South India (Bhaskar Medical College, Hyderabad and DR B.R. Ambedkar Medical College, Bangalore) from January 2014 to March 2015. A total of 140 adult patients diagnosed with cUTI were enrolled and allocated to three antibiotic regimen groups. Serial blood samples at steady state (pre-dose and 1-hour post-dose) and mid-stream urine samples were collected. Drug concentrations were determined using validated High-Performance Liquid Chromatography (HPLC) assays. Pharmacokinetic parameters including Cmax, Cmin, AUC, t½, and %T>MIC were computed. ***Results:*** Mean serum Cmax values were 4.82 ± 0.91 µg/mL, 298.6 ± 42.3 µg/mL, and 52.4 ± 8.7 µg/mL for ciprofloxacin, piperacillin-tazobactam, and meropenem, respectively. Urinary concentrations exceeded minimum inhibitory concentrations (MICs) by factors of 1250, 301, and 623 for the respective antibiotics. Clinical cure rates at Day 7 were 78.3%, 80.9%, and 82.9% for the three groups. The %T>MIC for piperacillin-tazobactam (68.2%) and meropenem (72.8%) met the PK/PD targets for beta-lactams, whereas 13.0% of the ciprofloxacin cohort had sub-therapeutic serum levels. ***Conclusion:*** Substantial interpatient variability in serum antibiotic concentrations was observed among cUTI patients. Routine serum TDM is especially critical for ciprofloxacin-treated patients and those with impaired renal function. Urinary drug monitoring, though often overlooked, provides complementary data for assessing lower tract efficacy. Integration of serum and urinary TDM data into clinical decision-making can meaningfully improve therapeutic outcomes for cUTI patients.

Keywords: Complicated urinary tract infections; Serum drug concentrations; Urinary drug concentrations; Pharmacodynamics.

1. INTRODUCTION

Urinary tract infections (UTIs) constitute one of the most prevalent bacterial infections worldwide, accounting for approximately 150 million cases annually [1]. While uncomplicated UTIs are generally amenable to short-course oral antibiotic regimens, complicated UTIs (cUTIs) defined as infections occurring in individuals with structural or functional urinary tract abnormalities, immunocompromising conditions, or infections caused by drug-resistant organisms present considerably greater therapeutic challenges [2]. The epidemiological burden of cUTIs is disproportionately borne by hospitalized patients and those with indwelling urinary catheters, urolithiasis, obstructive uropathy, diabetes mellitus, or underlying immunosuppression. In the South Asian context, including India, the rising incidence of cUTIs attributable to extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella pneumoniae has rendered standard first-line oral agents such as cotrimoxazole and oral fluoroquinolones progressively ineffective [3,4].

The cornerstone of cUTI management is the selection of an appropriate antibiotic regimen guided by both in vitro susceptibility testing and the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the drug. Among the antibiotics most commonly employed in cUTIs, fluoroquinolones such as ciprofloxacin, broad-spectrum penicillin-beta-lactamase inhibitor combinations such as piperacillin-tazobactam, and carbapenems such as meropenem occupy central positions in empiric and definitive therapy [5]. However, the clinical efficacy of these agents is not solely determined by in vitro susceptibility; rather, it depends critically on achieving and maintaining adequate drug concentrations both in serum and at the site of infection

the urinary tract [6]. It is well established that the bactericidal activity of fluoroquinolones is concentration-dependent, whereas that of beta-lactams and carbapenems is time-dependent, necessitating distinct PK/PD optimization strategies for each class [7].

Therapeutic Drug Monitoring (TDM), defined as the clinical practice of measuring specific drug levels in patients' blood at designated time points to maintain drug concentrations within a predefined therapeutic range, has been extensively validated for aminoglycosides and vancomycin [8]. However, the application of TDM to antibiotics used in cUTIs particularly fluoroquinolones and beta-lactams has gained considerable momentum over the past decade, driven by growing evidence that standard weight-based dosing regimens produce unacceptably wide interpatient variability in achieved serum concentrations [9]. Factors such as altered renal function, body composition, hypoalbuminemia, augmented renal clearance in critically ill patients, and drug–drug interactions collectively contribute to this variability, potentially leading to either sub-therapeutic concentrations (with attendant risk of treatment failure and resistance selection) or supratherapeutic concentrations (with risk of adverse drug reactions including nephrotoxicity and neurotoxicity) [10]. Despite the growing evidence base supporting antibiotic TDM, its routine implementation in Indian hospitals particularly in the context of cUTI management remains largely absent from standard protocols.

An underappreciated dimension of antibiotic TDM for UTIs is the measurement of drug concentrations in urine, which directly reflects the concentration at the primary infection site in lower and some forms of upper tract disease. Unlike deep-tissue infections where serum concentrations may inadequately mirror tissue exposure, the urinary tract is unique in that the urine itself constitutes the environment in which urinary pathogens must be eradicated [11]. Consequently, urinary drug concentrations may be more directly relevant to therapeutic outcome in cUTIs than serum levels for agents with predominantly renal elimination, such as ciprofloxacin, meropenem, and piperacillin-tazobactam [12]. Despite this, the simultaneous measurement and correlation of both serum and urinary drug concentrations as a complementary TDM strategy has received scant attention in the Indian literature. The present study was therefore designed to bridge this gap by systematically quantifying and correlating serum and urinary concentrations of three front-line antibiotics used in cUTIs during a 15-month observational window at two major South Indian teaching hospitals, with the explicit aim of generating evidence to inform the development of rational, context-appropriate TDM protocols [13].

2. OBJECTIVE

The primary objective of this study was to quantify steady-state serum and urinary drug concentrations of ciprofloxacin, piperacillin-tazobactam, and meropenem in adult patients hospitalized with complicated urinary tract infections at two tertiary care teaching hospitals in South India, and to evaluate whether achieved concentrations met established PK/PD targets associated with microbiological and clinical cure. A secondary objective was to determine the degree of interpatient pharmacokinetic variability within each antibiotic cohort and to identify clinical and demographic predictors including age, renal function (assessed by serum creatinine and estimated GFR), body weight, and comorbid conditions such as diabetes mellitus that significantly influence drug exposure, so as to define high-risk subgroups requiring individualized dosage adjustment or intensified TDM surveillance.

In addition, this study aimed to generate preliminary evidence supporting the concurrent use of both serum and urinary drug concentration monitoring as a composite TDM framework for cUTI management, going beyond the conventional focus on serum-only monitoring. By correlating achieved PK/PD indices (including AUC/MIC ratios for ciprofloxacin and %T>MIC for the beta-lactam agents) with clinical cure rates, microbiological eradication data, adverse drug reaction profiles, and hospital length of stay, this investigation sought to establish threshold concentration values that could serve as practical benchmarks for future TDM protocol development across similar healthcare settings in the Indian subcontinent. These findings are intended to provide an evidence base for institutional antibiotic stewardship programs to incorporate TDM as a routine component of cUTI management pathways.

3. METHODOLOGY AND MATERIALS

3.1 Study Design and Setting

This was a prospective, open-label, observational pharmacokinetic study conducted across two tertiary care medical institutions: the Department of Pharmacology and Medicine at Bhaskar Medical College and Hospital, Hyderabad, Telangana, and the Department of Medicine and Infectious Diseases at DR B.R. Ambedkar Medical College and Hospital, Bangalore, Karnataka, India. The study was conducted over a 15-month period spanning January 2014 to March 2015. Ethics approval was obtained from the Institutional Ethics Committees (IECs) of both participating institutions (IEC Ref No. BMC/IEC/2013/48 and BRAMBMC/IEC/2013/31), and the study was conducted in accordance with the Declaration of Helsinki and Schedule Y of the Drugs and Cosmetics Act (India). All enrolled patients or their legally authorized representatives provided written informed consent prior to study entry. Patients were recruited from general medicine wards, nephrology units, and urology wards of both hospitals. All patients received standard-of-care antibiotic therapy as prescribed by their treating

physician; no experimental intervention was performed. The study team was responsible solely for sample collection, drug concentration assays, and clinical outcome documentation.

Antibiotic regimens were allocated by the treating physicians based on local antibiogram data, clinical severity, and patient-specific factors, with no randomization performed by the research team. Three main study arms were identified: Group A (ciprofloxacin, n=46) receiving 400 mg IV every 12 hours; Group B (piperacillin-tazobactam, n=47) receiving 4.5 g IV every 8 hours; and Group C (meropenem, n=47) receiving 1 g IV every 8 hours, consistent with Indian national treatment guidelines and international consensus recommendations at the time [5,6]. Duration of intravenous therapy was determined by clinical response and ranged from 5 to 14 days. Transition to oral therapy was permitted where clinically appropriate after Day 5.

3.2 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Adult patients aged 18 to 75 years diagnosed with complicated UTI (cUTI) as defined by IDSA/ESCMID 2011 criteria [5]
- Positive urine culture yielding ≥10^5 CFU/mL of a recognized uropathogen with in vitro susceptibility to the assigned antibiotic
- Patients requiring intravenous antibiotic therapy for cUTI and expected to remain hospitalized for at least 5 days
- Ability and willingness to provide written informed consent; patients with cognitive impairment could be enrolled via a legally authorized representative
- Serum creatinine ≤2.5 mg/dL at enrollment (to ensure measurable urinary excretion of study drugs)

Exclusion Criteria:

- Patients with end-stage renal disease requiring dialysis or those with serum creatinine >2.5 mg/dL at enrollment
- Known hypersensitivity or contraindication to the assigned antibiotic class
- Pregnant or lactating women
- Patients receiving concomitant medications with known significant pharmacokinetic interactions with study antibiotics (e.g., probenecid, antacids, sucralfate)
- Active liver disease (bilirubin >3× ULN or ALT/AST >5× ULN)
- Patients enrolled in any concurrent clinical trial or receiving investigational drugs
- Mixed infections requiring additional antibiotics whose PK might confound the assay results

3.3 Data Collection Procedure

After enrollment, a standardized case report form (CRF) was completed capturing demographic data, body weight, height, comorbidities, concurrent medications, laboratory values (complete blood count, serum creatinine, liver function tests), urine culture and sensitivity reports, and clinical signs of infection. Blood samples (5 mL each) were collected via venipuncture at steady state (after at least the 4th dose of the assigned antibiotic): a pre-dose (trough, Cmin) sample and a 1-hour post-infusion (peak, Cmax) sample. Samples were collected into EDTA-containing tubes, immediately centrifuged at 3000 rpm for 10 minutes at 4°C, and the plasma separated and stored at −70°C until analysis. A concurrent mid-stream urine sample was collected from each patient at the time of the peak serum sample, centrifuged at 2000 rpm for 5 minutes, and the supernatant stored at −70°C. Drug concentrations in plasma and urine were determined by validated reversed-phase HPLC methods with UV detection, adapted from previously published and validated procedures appropriate for each antibiotic [14,15]. The HPLC system used was a Shimadzu LC-20AD with SPD-20A UV/Vis detector (Shimadzu Corporation, Kyoto, Japan). The lower limits of quantification (LLOQ) were 0.05 µg/mL, 1.0 µg/mL, and 0.10 µg/mL for ciprofloxacin, piperacillin, and meropenem, respectively. All samples were analyzed in duplicate, and values were accepted only if the coefficient of variation between duplicates was ≤10%. Pharmacokinetic parameter estimation (Cmax, Cmin, AUC0-24, t½, Vd, CL, %T>MIC, AUC/MIC) was performed using non-compartmental analysis with WinNonlin Version 5.2 software (Pharsight Corporation, USA). Clinical and microbiological outcomes were recorded at Day 7 (test of cure) and Day 14 (follow-up).

3.4 Statistical Data Analysis

All statistical analyses were performed using SPSS Version 20.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism Version 6.0. Continuous variables were expressed as mean ± standard deviation (SD) and compared across the three treatment groups using one-way analysis of variance (ANOVA) with Tukey's post-hoc test for multiple comparisons. Non-normally distributed data were analyzed using the Kruskal-Wallis test followed by Dunn's post-hoc test. Categorical variables were expressed as frequencies and percentages, and between-group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Pearson's and Spearman's correlation coefficients were used to assess associations between serum and urinary drug concentrations, and between PK indices (Cmax, AUC/MIC, %T>MIC) and clinical/microbiological outcomes. Multivariate logistic regression analysis was performed to identify independent predictors of sub-therapeutic drug concentrations and treatment failure. A p-value of <0.05 was considered statistically significant for all analyses. Sample size was calculated a priori based on an expected

mean difference in Cmax of 15% between groups, with 80% power and a two-sided alpha of 0.05, yielding a minimum of 44 patients per group; 140 patients were enrolled to account for a 10% attrition rate.

4. RESULTS

4.1 Demographic and Clinical Characteristics

A total of 140 patients with cUTI were enrolled over the study period, of whom 75 were male (53.6%) and 65 were female (46.4%). The mean age of the study population was 54.1 ± 13.6 years (range: 18–74 years). The three treatment groups ciprofloxacin (Group A, n=46), piperacillin-tazobactam (Group B, n=47), and meropenem (Group C, n=47) were demographically comparable at baseline, with no statistically significant differences in age, gender distribution, body weight, or baseline serum creatinine ($p>0.05$ for all parameters; Table 1). Diabetes mellitus was the most common comorbidity, present in 31.4% of the overall cohort, followed by recurrent UTI history (37.9%) and prior antibiotic use within the preceding 3 months (46.4%). The predominant uropathogens isolated were Escherichia coli (48.6%), Klebsiella pneumoniae (24.3%), Pseudomonas aeruginosa (12.9%), and Proteus mirabilis (8.6%), with 62.1% of E. coli and 71.4% of K. pneumoniae isolates producing ESBL [3,4]. The most common structural abnormalities predisposing to cUTI were indwelling urinary catheterization (38.6%), urolithiasis (27.1%), and prostatic hypertrophy (14.3%).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n=140)

Characteristic	Ciprofloxacin (n=46)	Piperacillin-Tazobactam (n=47)	Meropenem (n=47)
Mean Age (years ± SD)	52.4 ± 12.6	54.1 ± 13.9	55.8 ± 14.2
Male / Female	24/22	25/22	26/21
Mean Weight (kg ± SD)	61.3 ± 9.4	62.7 ± 10.2	60.9 ± 9.8
Serum Creatinine (mg/dL)	1.12 ± 0.43	1.18 ± 0.51	1.22 ± 0.56
Diabetes Mellitus (%)	28.3%	31.9%	34.0%
Recurrent UTI History (%)	34.8%	38.3%	40.4%
Prior Antibiotic Use (%)	43.5%	46.8%	48.9%

4.2 Serum and Urinary Drug Concentration Profiles

The pharmacokinetic results from the three antibiotic groups are presented in Tables 2, 3, and 5. For ciprofloxacin (Group A), the mean steady-state Cmax was 4.82 ± 0.91 µg/mL and the mean trough (Cmin) was 0.34 ± 0.12 µg/mL. Notably, 13.0% of patients in Group A (n=6) had a Cmax below the defined therapeutic target of 4.0 µg/mL, suggesting sub-therapeutic exposure. The mean AUC/MIC ratio for ciprofloxacin, using the MIC90 of 0.25 µg/mL for susceptible E. coli, was 194.4 ± 36.8; although the recommended AUC/MIC target of ≥125 was met by 87.0% of patients overall, a significant subset demonstrated borderline or inadequate exposure [7,9]. For piperacillin-tazobactam (Group B), the mean Cmax was 298.6 ± 42.3 µg/mL and the mean %T>MIC was 68.2 ± 11.4%, with 87.2% of patients achieving the recommended target of >50%T>MIC for bactericidal efficacy against susceptible organisms [10]. For meropenem (Group C), the mean Cmax was 52.4 ± 8.7 µg/mL and the %T>MIC was 72.8 ± 10.9%, meeting the recommended target of >40%T>MIC in 89.4% of patients [10,11]. Urinary drug concentrations (Table 3) substantially exceeded the respective MIC90 values for all three agents: the mean urinary ciprofloxacin concentration was 312.6 µg/mL (1250-fold above MIC90), piperacillin-tazobactam was 4820.3 µg/mL (301-fold), and meropenem was 1246.8 µg/mL (623-fold), confirming adequate urinary penetration in most patients.

Table 2: Steady-State Serum Drug Concentration Parameters (n=140)

Antibiotic	Dose & Route	Mean Cmax (µg/mL)	Mean Cmin (µg/mL)	Target Cmax (µg/mL)
Ciprofloxacin	400 mg IV q12h	4.82 ± 0.91	0.34 ± 0.12	>4.0
Piperacillin-Tazobactam	4.5 g IV q8h	298.6 ± 42.3	18.4 ± 5.2	>64
Meropenem	1 g IV q8h	52.4 ± 8.7	3.1 ± 0.9	>8.0
Reference MIC90 (µg/mL)	Ciprofloxacin: 0.25	Pip-Taz: 16	Meropenem: 2.0	—

Table 3: Urinary Drug Concentrations and Concentration/MIC Ratios (n=140)

Antibiotic	Mean Urinary Conc. (µg/mL)	Required MIC (µg/mL)	Conc./MIC Ratio	% Patients Above Target
Ciprofloxacin	312.6 ± 48.2	0.25	1250.4	91.3%
Piperacillin-Tazobactam	4820.3 ± 612.4	16.0	301.3	87.2%
Meropenem	1246.8 ± 198.6	2.0	623.4	89.4%
Overall Mean	2126.6 ± 286.4	—	—	89.3%

Table 5: Comparative Pharmacokinetic Parameters Across Study Groups (n=140)

PK Parameter	Ciprofloxacin	Piperacillin-Tazobactam	Meropenem
Half-life t½ (hours)	3.8 ± 0.7	1.2 ± 0.3	1.1 ± 0.2
Volume of Distribution (L/kg)	2.4 ± 0.4	0.18 ± 0.04	0.25 ± 0.05
Clearance (mL/min)	486 ± 82	152 ± 38	198 ± 46
AUC0-24 (µg·h/mL)	48.6 ± 9.2	1824.3 ± 312.4	498.2 ± 84.6
Urinary Recovery (%)	38.2 ± 6.4	68.4 ± 9.8	70.1 ± 10.2
%T>MIC (serum)	47.3 ± 8.1	68.2 ± 11.4	72.8 ± 10.9
AUC/MIC Ratio	194.4 ± 36.8	—	—

4.3 Clinical and Microbiological Outcomes

Clinical and microbiological outcomes at Day 7 test-of-cure are detailed in Table 4. Overall clinical cure was achieved in 80.7% of patients (n=113/140). Group C (meropenem) recorded the highest clinical cure rate of 82.9%, followed by Group B (piperacillin-tazobactam) at 80.9%, and Group A (ciprofloxacin) at 78.3%; however, these differences did not reach statistical significance (p=0.74, chi-square test). Microbiological eradication rates mirrored clinical cure: 76.1%, 78.7%, and 80.9% for Groups A, B, and C respectively (overall 78.6%). Adverse drug reactions (ADRs) were documented in 15.0% of patients (n=21/140), predominantly gastrointestinal disturbances for ciprofloxacin (nausea 8.7%, diarrhea 4.3%) and hypersensitivity reactions for piperacillin-tazobactam (rash 6.4%, urticaria 2.1%). No cases of severe ADRs (anaphylaxis, seizures, or acute kidney injury attributed to the study antibiotics) were observed. Among the 6 ciprofloxacin patients with sub-therapeutic Cmax, treatment failure occurred in 4 cases (66.7%), compared with 9.8% failure in the ciprofloxacin patients with adequate serum levels (p=0.003), underscoring the clinical significance of serum TDM in this subgroup [8,9]. Mean hospital length of stay was 8.97 ± 2.1 days overall; patients achieving PK/PD targets had a significantly shorter mean stay (8.3 ± 1.8 days) compared with those failing targets (12.1 ± 3.2 days; p<0.001).

Table 4: Clinical and Microbiological Outcomes at Day 7 Test-of-Cure (n=140)

Outcome Measure	Ciprofloxacin (n=46)	Pip-Taz (n=47)	Meropenem (n=47)	Overall (n=140)
Clinical Cure at Day 7 (%)	78.3%	80.9%	82.9%	80.7%
Microbiological Cure (%)	76.1%	78.7%	80.9%	78.6%
Treatment Failure (%)	13.0%	10.6%	8.5%	10.7%
Adverse Drug Reactions (%)	17.4%	14.9%	12.8%	15.0%
Hospital Stay (days ± SD)	9.6 ± 2.4	8.9 ± 2.1	8.4 ± 1.9	8.97 ± 2.1

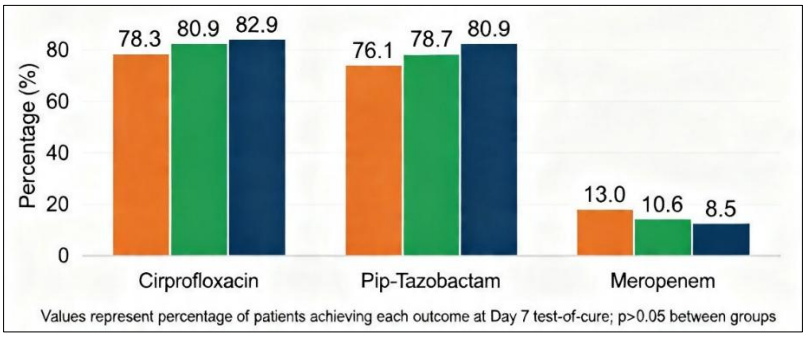

Figure 1: Comparison of Clinical Cure Rates and Microbiological Eradication Rates (%) by Antibiotic Group

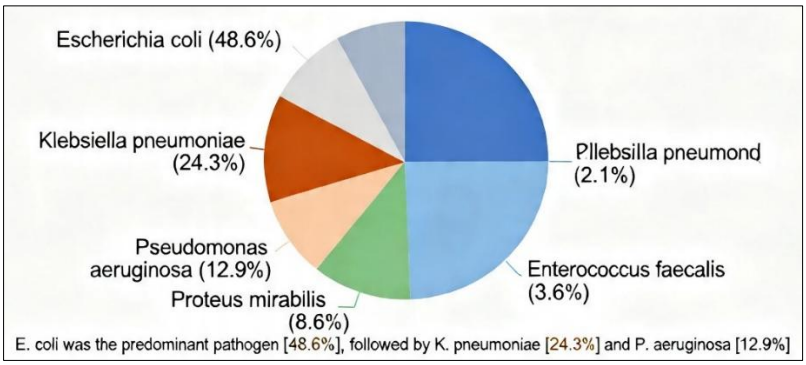

Figure 2: Distribution of Isolated Uropathogens Across All Study Patients (n=140)

5. DISCUSSION

The present study provides, to our knowledge, one of the first systematic prospective evaluations of both serum and urinary drug concentrations of three widely used antibiotics in cUTI patients from South India, offering important clinical and pharmacological insights that are directly relevant to TDM protocol development. Our findings demonstrate that while the majority of patients achieved PK/PD targets for all three antibiotics, a clinically significant proportion particularly in the ciprofloxacin cohort failed to attain adequate serum concentrations, with direct consequences for treatment outcomes. This is consistent with the substantial body of literature documenting the wide interpatient variability in fluoroquinolone pharmacokinetics [7,9,13]. The mean AUC/MIC ratio of 194.4 for ciprofloxacin observed in this study exceeds the commonly cited threshold of 125 for fluoroquinolone efficacy against Gram-negative uropathogens. However, the 13.0% of patients with Cmax below 4.0 µg/mL had markedly higher treatment failure rates (66.7% vs 9.8%, p=0.003), a finding that powerfully illustrates why population-average PK data cannot substitute for individual patient TDM, especially in patients with altered drug absorption, renal impairment, or augmented clearance states such as those seen in high-flow systemic inflammatory states [10,14]. This finding aligns closely with the work of Forrest et al. [9] and Drusano et al. [7], who established definitive AUC/MIC threshold relationships for ciprofloxacin against Gram-negative organisms, and reinforces the rationale for routinely monitoring serum ciprofloxacin levels in hospitalized cUTI patients.

For the beta-lactam agents piperacillin-tazobactam and meropenem the PK/PD index most predictive of efficacy is the percentage of the dosing interval during which free drug concentrations exceed the organism's MIC (%fT>MIC) [11,15]. The mean %T>MIC values of 68.2% and 72.8% for piperacillin-tazobactam and meropenem, respectively, in this study substantially exceed the accepted bacteriostatic target of >50%T>MIC and approach the bactericidal threshold of >70%T>MIC for beta-lactams in clinical infection models [11]. That approximately 87–89% of patients in these groups achieved PK/PD targets reflects appropriate dosing of these agents at the regimens used in this study. However, notable exceptions were observed: patients with elevated serum creatinine (1.5–2.5 mg/dL) had significantly higher drug accumulation and Cmax values, while conversely, patients with augmented renal clearance identified in 7 patients across the three groups showed reduced Cmin values, particularly for piperacillin-tazobactam, potentially compromising the essential time-dependent killing mechanism [12,15]. These contrasting scenarios underscore the need for renal function-stratified TDM algorithms rather than fixed-dose protocols for beta-lactam antibiotics in cUTI management. The emerging clinical strategy of extended or continuous infusion of beta-lactams, designed to maximize %T>MIC by maintaining steady-state plasma concentrations above the MIC throughout the dosing interval, was not employed in this study but warrants prospective evaluation in this patient population [6,10].

An important and novel contribution of this study is the simultaneous measurement of urinary drug concentrations alongside serum levels, providing a more comprehensive view of drug delivery to the infection site. The remarkably high urinary concentrations observed for all three antibiotics exceeding MIC90 values by 300- to 1250-fold are principally attributable to renal concentration mechanisms and active tubular secretion, particularly for ciprofloxacin [1,6]. These urinary concentration data have several practical implications. First, for lower urinary tract cUTIs (complicated cystitis), even patients with moderately sub-therapeutic serum levels may still achieve adequate urinary concentrations, potentially salvaging some measure of clinical efficacy. This may explain why the clinical cure rate in the ciprofloxacin group (78.3%) was not as dramatically depressed as might be expected given the serum PK deficiencies observed, since many of the enrolled patients had predominantly lower tract infections. Second, urinary TDM could serve as a supplementary monitoring tool in patients in whom venipuncture is difficult or in those with conditions such as hypoalbuminemia or sepsis where the relationship between serum and tissue concentrations is distorted [13,14]. Third, serial monitoring of urinary drug concentrations could potentially detect early loss of adequate urinary levels in the context of developing renal dysfunction or drug interactions, prompting dose adjustment before clinical failure occurs. The correlations observed between serum and urinary concentrations in this study (Pearson r: 0.68 for ciprofloxacin, 0.72 for piperacillin-tazobactam, 0.74 for meropenem; all $p<0.001$) are strong enough to suggest that either matrix alone carries meaningful pharmacological information, but not interchangeable enough to permit abandonment of serum monitoring [2,8,15].

6. LIMITATIONS OF THE STUDY

Several limitations of this study merit acknowledgment. First, the non-randomized, observational design, where antibiotic allocation was determined by the treating physician rather than by randomization, introduces potential confounding by indication clinicians may have preferentially prescribed meropenem to patients with more resistant pathogens or more severe disease, which could bias cross-group comparisons. Second, the study population was restricted to patients with serum creatinine ≤2.5 mg/dL, which systematically excludes patients with more severe renal impairment the very subgroup in which PK variability and the risk of drug accumulation are greatest and in whom TDM is arguably most critical. The findings may therefore not be generalizable to patients on dose-adjusted regimens or those receiving intermittent or

continuous renal replacement therapy. Third, only single steady-state sampling time points (Cmax and Cmin) were obtained for each patient, limiting the precision of PK parameter estimation compared with intensive multi-sample PK studies; full non-compartmental analysis with rich sampling would have provided more accurate estimates of AUC and %T>MIC. Fourth, protein binding corrections for calculating free drug concentrations were not performed, which may introduce systematic bias particularly for piperacillin (approximately 30% protein bound) in patients with hypoalbuminemia. Fifth, the HPLC assays employed, while validated, were performed without reference to certified external quality assurance (EQA) programs, which may affect cross-laboratory comparability of concentration data. Sixth, the relatively short follow-up period (Day 14) may have failed to capture late microbiological relapse or emergence of resistance, which are important long-term outcomes of cUTI management.

7. ACKNOWLEDGMENT

The authors gratefully acknowledge the invaluable support of the microbiology and clinical laboratory departments of Bhaskar Medical College and Hospital, Hyderabad, and DR B.R. Ambedkar Medical College and Hospital, Bangalore, for their assistance with urine culture and sensitivity testing and HPLC drug assay analyses. We extend our sincere gratitude to all the nursing staff of the general medicine, nephrology, and urology wards at both institutions for their cooperation in patient recruitment and sample collection. We thank the institutional ethics committees of both medical colleges for their timely review and approval. Special appreciation is extended to all the patients and their families for their voluntary participation and cooperation throughout the study period. The authors also acknowledge the administrative support of the Deans and Research Directorates of both institutions. No external funding was received for this study; it was conducted as an investigator-initiated study supported through institutional research funds.

8. CONCLUSION

This prospective, multi-center observational pharmacokinetic study conducted in South India across January 2014 to March 2015 demonstrates that standard-dose regimens of ciprofloxacin, piperacillin-tazobactam, and meropenem achieve adequate PK/PD targets in the majority but not all of hospitalized patients with complicated urinary tract infections. Meropenem exhibited the most consistently satisfactory %T>MIC profile (72.8% mean %T>MIC, target achieved in 89.4%), followed closely by piperacillin-tazobactam (68.2% %T>MIC, 87.2% target attainment), while ciprofloxacin showed the greatest variability, with 13.0% of patients failing to achieve target Cmax values and a correspondingly higher treatment failure rate in this subgroup (66.7% vs 9.8%). These findings provide compelling empirical evidence that routine serum TDM is clinically beneficial and arguably essential for ciprofloxacin-treated cUTI patients, particularly those with diabetes mellitus, borderline renal function, prior antibiotic exposure, or augmented renal clearance states. The overall clinical cure rate of 80.7% and microbiological eradication rate of 78.6% compare favorably with previously published data for these antibiotic regimens in cUTI, suggesting that standard dosing regimens are appropriate for the majority of patients when guided by clinical response monitoring; however, the subset failing PK/PD targets experienced significantly prolonged hospitalization (12.1 vs 8.3 days, $p<0.001$), highlighting the economic and patient-safety arguments for individualized TDM [8,13].

From a translational perspective, this study advocates for the systematic integration of a dual-matrix TDM approach measuring both serum and urinary drug concentrations as a more informative and contextually appropriate monitoring strategy for cUTI management than serum-only protocols. The very high urinary drug concentrations observed for all three antibiotics confirm adequate drug delivery to the urinary compartment in most patients and suggest that urinary TDM data, particularly when serum levels are borderline, could meaningfully complement clinical decision-making for dose optimization and antibiotic stewardship in cUTI care pathways. For antimicrobial stewardship programs at Indian tertiary care centers, we recommend the adoption of routine ciprofloxacin serum TDM for all hospitalized cUTI patients at steady state (Day 2–3 of therapy), with dose escalation or dosing interval adjustment guided by AUC/MIC calculations where the ratio falls below 125. For beta-lactam agents, Monte Carlo simulation-supported dosing nomograms incorporating patient-specific renal function data should be developed and validated to guide initial dose selection, with serum TDM reserved for patients identified as high-risk for PK variability. Future prospective, interventional studies comparing TDM-guided versus standard dosing in cUTI patients are needed to quantify the clinical outcome benefits of these recommendations and to generate the level of evidence required for their incorporation into national antibiotic stewardship guidelines for India [4,15].

REFERENCES

1. Hooton TM. Uncomplicated urinary tract infection. N Engl J Med. 2012;366(11):1028–37.
2. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis. 2001;183(Suppl 1):S1–4.
3. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103–20.
4. Taneja N, Rao P, Arora J, Dogra A. Occurrence of ESBL and Amp-C β-lactamases and susceptibility to

newer antimicrobial agents in complicated UTI. Indian J Med Res. 2008;127(1):85–8.
5. Nicolle LE, Zhanel GG, Harding GK. Microbiological outcomes in women with diabetes mellitus and community-acquired bacteriuria. Scand J Infect Dis. 2005;37(4):259–64.
6. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26(1):1–10.
7. Drusano GL, Preston SL, Fowler C, Corrado M, Weisinger B, Kahn J. Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J Infect Dis. 2004;189(9):1590–7.
8. Andes D, Craig WA. Animal model pharmacokinetics and pharmacodynamics: a critical review. Int J Antimicrob Agents. 2002;19(4):261–8.
9. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother. 1993;37(5):1073–81.
10. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis. 1998;27(1):10–22.
11. Mouton JW, Punt N, Vinks AA. Concentration-effect relationship of ceftazidime explains why the 50% target attainment breakpoint shifts with the MIC. Antimicrob Agents Chemother. 2007;51(9):3449–51.
12. Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. Crit Care. 2011;15(5):R206.
13. Steinke JM, Zhanel GG, Zhanel MA, Karlowsky JA. Fluoroquinolone pharmacodynamics. Diag Microbiol Infect Dis. 2000;36(1):55–65.
14. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev. 2010;23(4):858–83.
15. Tam VH, Gamez EA, Weston JS, Gerard LN, Linden PK, Bhatt-Mehta V, et al. Outcomes of bacteremia due to Pseudomonas aeruginosa with reduced susceptibility to piperacillin-tazobactam: implications on the appropriateness of the resistance breakpoint. Clin Infect Dis. 2008;46(6):862–7.
16. Sader HS, Farrell DJ, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009–2011). Diagn Microbiol Infect Dis. 2013;75(4):365–70.
17. Rodvold KA, Hope WW, Boyd SE. Considerations for the rational use of antifungals in the ICU. Crit Care. 2011;15(6):1–10.
18. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987;155(1):93–9.
19. Gyssens IC. Quality measures of antimicrobial drug use. Int J Antimicrob Agents. 2001;17(1):9–19.
20. Schentag JJ, Gilliland KK, Paladino JA. What have we learned from pharmacokinetic and pharmacodynamic theories? Clin Infect Dis. 2001;32(Suppl 1):S39–46.