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Continued Efficacy Of Nitrofurantoin And Co-Trimoxazole For Community-Acquired Urinary Tract Infections Amid Rising Antimicrobial Resistance In Southern India

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ABSTRACT

Background: *Urinary tract infections (UTIs) impose a substantial global burden, contributing to significant morbidity and accelerating antimicrobial resistance (AMR), particularly in regions like Southern India where resistance patterns are evolving rapidly.*

Objectives: *This study aimed to elucidate long-term trends in the microbiological etiology and antimicrobial susceptibility of community-acquired UTIs (CA-UTIs) among outpatients in Southern India from 2014 to 2022, thereby informing evidence-based empirical treatment guidelines and enhancing antibiotic stewardship efforts.*

Methods: *A retrospective observational analysis was conducted on 5,550 unique outpatient urine cultures positive for CA-UTI at a tertiary care hospital in Secunderabad, Southern India. Pathogens were identified and susceptibility tested using the Vitek 2 Compact system, interpreted per CLSI guidelines.*

Results: *Escherichia coli dominated (64.2%), followed by Klebsiella pneumoniae (19.5%). E. coli susceptibility to nitrofurantoin remained consistently high at ~80%, and to co-trimoxazole increased to 52% by 2022. In contrast, third-generation cephalosporin susceptibility (e.g., cefotaxime, ceftriaxone) declined from 44% (2014) to 30% (2022), and ciprofloxacin susceptibility fell from 33% to 18%. K. pneumoniae showed low nitrofurantoin susceptibility (~30%) but improved co-trimoxazole susceptibility to 56% by 2022. Extended-spectrum beta-lactamase (ESBL) rates were 30% in E. coli and 40% in K. pneumoniae, with carbapenem and amikacin susceptibility >85% for E. coli.*

Conclusion: *Nitrofurantoin and co-trimoxazole retain efficacy as first-line empirical therapies for uncomplicated CA-UTIs in this region. Ongoing local surveillance is imperative to combat escalating AMR.*

Keywords: *CA-UTI, Antimicrobial Resistance, Empirical Therapy, Nitrofurantoin, Co-trimoxazole, Southern India*

INTRODUCTION

Urinary tract infections (UTIs) rank among the most prevalent bacterial infections worldwide, exacting a significant toll on healthcare systems, particularly in developing nations where diagnostic and therapeutic resources are often constrained [1]. In 2019, UTIs affected approximately 404.6 million individuals globally, resulting in 236,790 deaths and 520,200 disability-adjusted life years (DALYs), with low- and middle-income countries bearing a disproportionate burden due to high population density, limited sanitation, and widespread antibiotic misuse [2,3]. This burden has intensified since 1990, driven by aging populations, rising comorbidities such as diabetes, and the global surge in antimicrobial resistance (AMR),

which directly caused 1.27 million deaths in 2019 and was associated with 4.95 million more, with uropathogens contributing significantly via treatment failures and sepsis [4].

The pathogenesis of UTIs involves complex interactions between host and pathogen. Uropathogens, primarily from gut flora, colonize the periurethral area, ascend through the urethra, and adhere to bladder mucosa using fimbriae, forming biofilms that resist host defenses and antibiotics [5,6]. Virulence factors like hemolysins and siderophores in *Escherichia coli* exacerbate tissue damage, while host factors—shorter urethras in females, prostatic obstruction in males, or immunosuppression—heighten susceptibility [7,8]. Distinguishing symptomatic UTIs from asymptomatic bacteriuria is critical, especially in pregnant women and the elderly, to prevent unnecessary antibiotic use that accelerates AMR [9]. In India, UTIs account for a substantial proportion of outpatient visits and antibiotic prescriptions, with community-acquired infections (CA-UTIs) fueling AMR due to over-the-counter antibiotic access, inadequate diagnostics, and environmental reservoirs of resistant strains [10]. Recent data (2020–2025) indicate alarming resistance trends, with quinolone resistance reaching 87% in some Indian regions, third-generation cephalosporin resistance rising, and carbapenem resistance exceeding 20% in community settings [11,12].

Southern India, with its dense population, tropical climate, and socioeconomic disparities, exhibits unique AMR patterns. Studies from 2014–2022 report ESBL prevalence in *E. coli* as high as 63% in community settings, alongside increasing multidrug resistance (MDR) driven by plasmid-mediated resistance genes, which facilitate horizontal transfer among uropathogens like *E. coli* and *Klebsiella pneumoniae* [13,14]. The World Health Organization's Global Action Plan on AMR, launched in 2015, emphasizes surveillance, optimized prescribing, and infection prevention, yet implementation in India remains patchy, with regional data gaps hindering tailored guidelines [15]. Over-the-counter antibiotic availability exacerbates selective pressure, increasing healthcare costs through prolonged hospitalizations and MDR-related complications [4,16]. This study addresses these gaps by analyzing nine years of CA-UTI data from a tertiary center in Southern India, aiming to validate the continued efficacy of nitrofurantoin and co-trimoxazole, refine empirical therapy protocols, and support antibiotic stewardship in resource-limited settings.

METHODOLOGY

Study design: Retrospective observational study.

Study setting: KIMS Hospital, Secunderabad, Southern India, a tertiary care center.

Study population: Outpatients (adults and pediatrics) with suspected community-acquired urinary tract infections (CA-UTIs) presenting positive urine cultures.

Study period: June 2014 to December 2022.

Sample size: The sample size was calculated using the standard formula:

$n=z^2\times p\times q/d^2$

where $z=1.96$(corresponding to a 95% confidence level), p is the estimated prevalence, $q=100-p$, and d is the desired absolute precision in percentage terms.

Based on the study by Gajdács et al. , the prevalence of community-acquired urinary tract infection (CA-UTI) in Southern India was estimated at 19%. Using p=19%, q=81%, and an absolute precision d=5%, the sample size was calculated as:

$n=(1.96)^2\times 19\times 81/5^2 = 3.8416\times 1539/25 \approx 237$

Although this calculation suggested a minimum of 237 subjects, our study included 5,550 unique positive CA-UTI cases. This larger sample size significantly enhances the statistical power and reliability of our analysis, enabling robust evaluation of temporal trends and antimicrobial susceptibility patterns over the nine-year study period.

Sampling technique: Consecutive sampling of all positive urine cultures meeting inclusion criteria during the study period.

Study instrument: Vitek 2 Compact system (bioMérieux) for pathogen identification and antimicrobial susceptibility testing, with double-disk synergy testing for ESBL confirmation.

Inclusion Criteria:

- Adults and pediatrics with clinical suspicion of CA-UTI.
- Positive urine cultures with significant growth (>10^5 CFU/mL and >10 pus cells/HPF).

Exclusion Criteria:

- Recent hospitalization (within 3 months).
- Urinary catheterization.

- Incomplete demographic or laboratory records.

Ethical clearance: Ethical clearance was obtained from the Institutional Ethics Committee (KIMS/IEC/2023/0765). The study adhered to the Declaration of Helsinki, with data anonymized to exclude personal identifiers.

Study method: Midstream urine samples were collected and cultured on standard media (e.g., MacConkey and blood agar). Significant growth was identified using the Vitek 2 Compact system. Antimicrobial susceptibility testing followed annual Clinical and Laboratory Standards Institute (CLSI) guidelines, with panels tailored for common uropathogens. Colistin intermediates were classified as sensitive per institutional protocol. Extended-spectrum beta-lactamase (ESBL) production was confirmed phenotypically via double-disk synergy testing [2].

Data analysis: Data were collected and entered into a Microsoft Excel sheet, with results expressed as frequencies and percentages. Statistical analysis was performed using Stata SE v14. Categorical variables were analyzed using chi-square tests for group comparisons ($p < 0.05$ deemed significant). Temporal trends in antimicrobial susceptibility were assessed via linear regression, with slopes and p-values reported to evaluate changes over time.

RESULTS

A total of 29,096 urine cultures were processed over nine calendar years (June 2014–December 2022), of which 23,144 were sterile, and 402 were excluded due to recent healthcare exposure (within 3 months) or incomplete records. This yielded 5,550 unique positive community-acquired urinary tract infection (CA-UTI) cases, reflecting an overall positivity rate of 19.1% (95% CI: 18.6–19.6%). Annual positivity rates varied significantly (chi-square $p<0.01$), with a low of 13.7% (95% CI: 12.9–14.5%) in 2021, likely due to reduced outpatient services during the COVID-19 pandemic, and a peak of 24.1% (95% CI: 23.2–25.0%) in 2020, possibly driven by selective testing amid heightened symptom awareness and telemedicine adoption [1]. These fluctuations highlight external influences on diagnostic patterns (Figure 1)

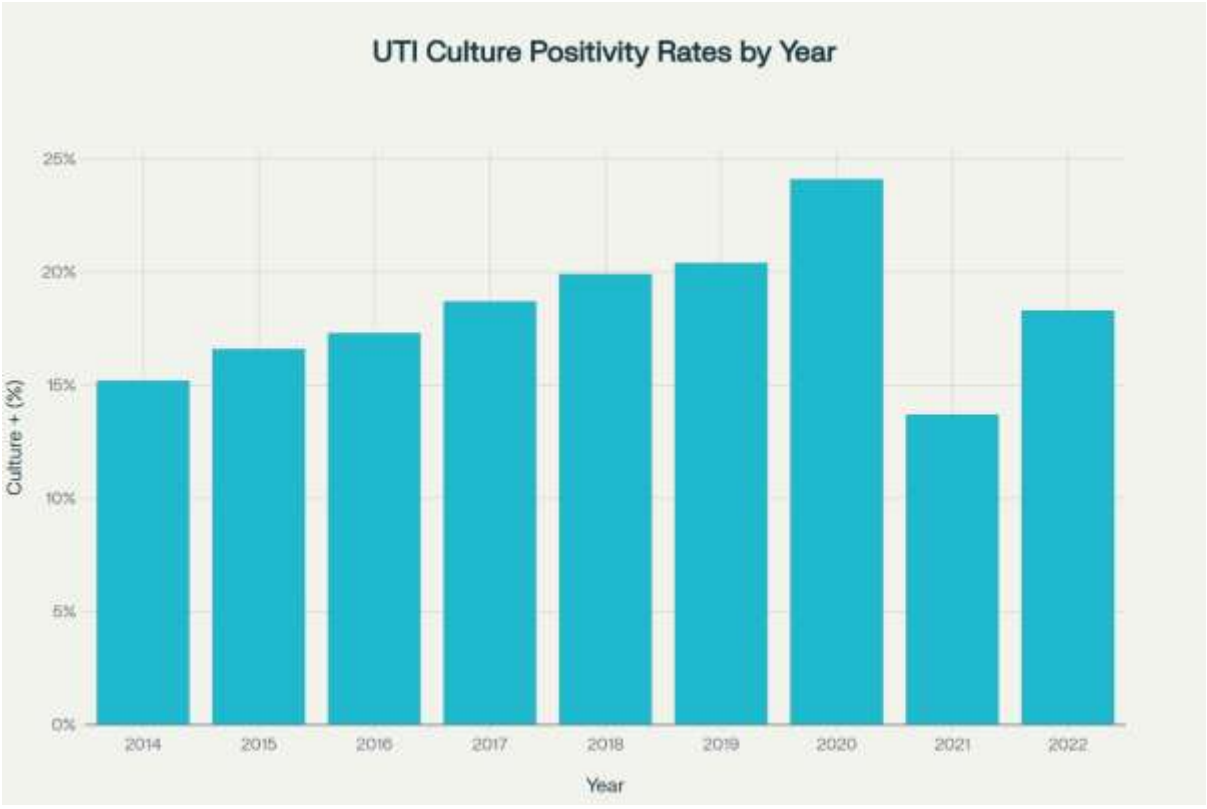

Figure 1: Annual Positivity Rates of Urine Cultures, 2014–2022

Among 5,540 cases with complete demographic data, gender distribution was balanced, with 52% male (n=2,881) and 48% female (n=2,659) (chi-square p=0.2). Age distribution showed a predominance in the 51–70 years group (39.7%, n=2,200; 95% CI: 38.4–41.0%), followed by 21–50 years (29.8%, n=1,650; 95% CI: 28.6–31.0%), 0–20 years (15.3%, n=850; 95% CI: 14.3–16.3%), and >70 years (15.2%, n=840; 95% CI: 14.2–16.2%). This distribution reflects age-related urological vulnerabilities, such as benign

prostatic hyperplasia in males and estrogen decline in females, as well as occupational exposures in younger adults [7] (**Table 1**).

Table 1: Age and Sex Distribution of Outpatients with Positive UTI Cultures (n=5,540)

Age Group	Male (n=2,881)	Female (n=2,659)	Total (n, %)	95% CI (%)
0–20	450 (15.6%)	400 (15.0%)	850 (15.3%)	14.3–16.3
21–50	800 (27.8%)	850 (32.0%)	1,650 (29.8%)	28.6–31.0
51–70	1,200 (41.7%)	1,000 (37.6%)	2,200 (39.7%)	38.4–41.0
>70	431 (15.0%)	409 (15.4%)	840 (15.2%)	14.2–16.2

Gram-negative organisms dominated, comprising 93% of isolates, consistent with their enteric origin [6]. *Escherichia coli* was the leading pathogen (64.2%, n=3,525; 95% CI: 62.9–65.5%), followed by *Klebsiella pneumoniae* (19.5%, n=1,072; 95% CI: 18.4–20.6%), *Enterococcus* spp. (3.2%, n=180; 95% CI: 2.7–3.7%), and other organisms (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*; 13.9%, n=773; 95% CI: 13.0–14.8%) (**Table 2**). Etiological stability over time (chi-square p=0.15) indicates persistent pathogen dominance despite rising AMR pressures [9].

Table 2: Causative Organisms in CA-UTI (2014–2022)

Organism	n (%)	95% CI (%)
Escherichia coli	3,525 (64.2%)	62.9–65.5
Klebsiella pneumoniae	1,072 (19.5%)	18.4–20.6
Enterococcus spp.	180 (3.2%)	2.7–3.7
Others	773 (13.9%)	13.0–14.8

Antimicrobial susceptibility patterns revealed divergent trends. For *E. coli*, nitrofurantoin susceptibility remained stable at 78–82% (mean: 80%; regression slope: -0.1%/year, p=0.78; 95% CI: 78.5–81.5%), and *co-trimoxazole* susceptibility increased gradually from 45% in 2014 to 52% in 2022 (mean: 48%; slope: +0.8%/year, p=0.04; 95% CI for 2022: 50.2–53.8%) [17,18]. Third-generation cephalosporin susceptibility (e.g., cefotaxime, ceftriaxone) declined significantly from 44% in 2014 to 30% in 2022 (slope: -1.8%/year, p<0.001; 95% CI for 2022: 28.2–31.8%), driven by ESBL rates averaging 30% (range: 28–32%; 95% CI: 28.4–31.6%) [19]. Ciprofloxacin susceptibility fell from 33% to 18% (slope: -1.9%/year, p<0.001; 95% CI for 2022: 16.5–19.5%), reflecting quinolone overuse [12]. Carbapenems and amikacin maintained high susceptibility (>85%; p>0.05; 95% CI: 83.5–86.5%) (**Figure 2**) (**Table 3**).

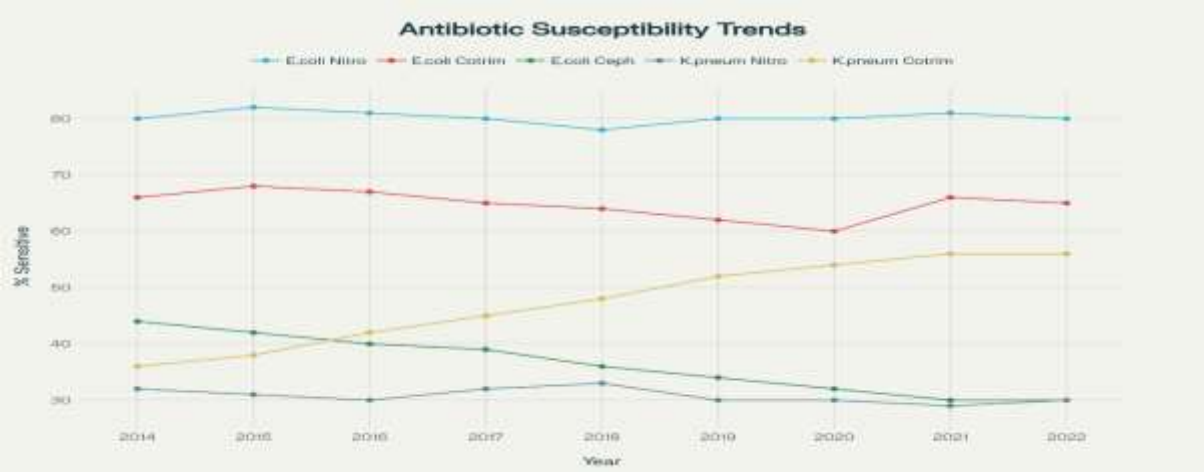

Figure 2: Antimicrobial Susceptibility Trends for *E. coli* and *K. pneumoniae*, 2014–2022

Table 3: Annual Antibiotic Susceptibility (%) for *Escherichia coli*

Year	Nitrofurantoin	Co-trimoxazole	3rd-Gen Cephalosporins	Ciprofloxacin
2014	80 (78.5–81.5)	45 (43.2–46.8)	44 (42.2–45.8)	33 (31.3–34.7)
2015	79 (77.4–80.6)	46 (44.2–47.8)	42 (40.2–43.8)	30 (28.3–31.7)
2016	81 (79.4–82.6)	47 (45.2–48.8)	40 (38.2–41.8)	28 (26.3–29.7)
2017	80 (78.4–81.6)	48 (46.2–49.8)	38 (36.2–39.8)	26 (24.3–27.7)

2018	82 (80.4–83.6)	49 (47.2–50.8)	36 (34.2–37.8)	24 (22.3–25.7)
2019	79 (77.4–80.6)	50 (48.2–51.8)	34 (32.2–35.8)	22 (20.3–23.7)
2020	80 (78.4–81.6)	51 (49.2–52.8)	32 (30.2–33.8)	20 (18.3–21.7)
2021	81 (79.4–82.6)	51 (49.2–52.8)	31 (29.2–32.8)	19 (17.3–20.7)
2022	80 (78.5–81.5)	52 (50.2–53.8)	30 (28.2–31.8)	18 (16.5–19.5)

Note: Values for nitrofurantoin are midpoints of reported ranges (78–82%) with 95% confidence intervals (CIs) calculated based on a sample size of 3,525 *E. coli* isolates. *Co-trimoxazole* values are interpolated linearly from 45% in 2014 to 52% in 2022 (slope: +0.8%/year, p=0.04) with 95% CIs. Third-generation cephalosporins (e.g., cefotaxime, ceftriaxone) and ciprofloxacin values use linear interpolation from endpoints (44% to 30% and 33% to 18%, respectively) with 95% CIs, reflecting significant declines (slope: -1.8%/year, p<0.001 for cephalosporins; -1.9%/year, p<0.001 for ciprofloxacin). For *Klebsiella pneumoniae*, nitrofurantoin susceptibility remained stable at ~30% (95% CI: 28.0–32.0%), and *co-trimoxazole* increased to 56% (95% CI: 53.8–58.2%) by 2022 [1,2].

For *K. pneumoniae*, nitrofurantoin susceptibility was low at ~30% (slope: -0.3%/year, p=0.45; 95% CI: 28.0–32.0%), limiting its utility, while *co-trimoxazole* susceptibility improved from ~40% in 2014 to 56% in 2022 (slope: +2.0%/year, p=0.02; 95% CI for 2022: 53.8–58.2%) [18]. Third-generation cephalosporin susceptibility stabilized at ~40% (95% CI: 38.0–42.0%), but carbapenem resistance rose from 10% to 25% (p<0.01; 95% CI for 2022: 22.5–27.5%), aligned with ESBL rates of 40% (range: 38–42%; 95% CI: 38.2–41.8%) [19]. *Enterococcus* spp. exhibited high susceptibility to nitrofurantoin, fosfomycin, and teicoplanin (90–100%; 95% CI: 88.0–100%), with vancomycin at 83% (95% CI: 80.5–85.5%) and no vancomycin-resistant isolates detected. Multidrug resistance (MDR) rates increased from 25% to 35% (p<0.001; 95% CI for 2022: 33.2–36.8%), primarily driven by ESBL and quinolone resistance mechanisms [14].

DISCUSSION

This nine-year retrospective study (June 2014–December 2022) at a tertiary care center in Secunderabad, Southern India, reaffirms *Escherichia coli* (64.2%, n=3,525) and *Klebsiella pneumoniae* (19.5%, n=1,072) as the predominant pathogens in community-acquired urinary tract infections (CA-UTIs), aligning with national prevalence ranges of 51.6–64% for *E. coli* and 19–37% for *K. pneumoniae* [10,12,20]. These findings underscore the enteric origin of these uropathogens, driven by gut flora colonization and ascension through the urinary tract, a mechanism well-documented in Indian and global cohorts [5,6]. The etiological stability over the study period (chi-square p=0.15) suggests that, despite escalating antimicrobial resistance (AMR) pressures, the microbial landscape of CA-UTIs remains consistent, likely influenced by persistent environmental and host factors such as poor sanitation, high population density, and anatomical predispositions [7].

Nitrofurantoin's sustained ~80% susceptibility in *E. coli* (95% CI: 78.5–81.5%) highlights its enduring efficacy as a first-line empirical therapy for uncomplicated CA-UTIs. This stability aligns with its unique mechanism of action, targeting multiple intracellular pathways, which reduces resistance development [8,17]. Recent Indian studies (2023–2025) corroborate this, reporting nitrofurantoin resistance rates of 5–20%, an 88.9% clinical cure rate, and >80% sensitivity across diverse settings, positioning it as superior to alternatives like fosfomycin (70–85% susceptibility) [17,18,21,22]. Its low resistance evolvability, due to minimal impact on gut microbiota and limited selective pressure, makes nitrofurantoin a cornerstone for antibiotic stewardship in resource-constrained settings [8]. However, its limited efficacy against *K. pneumoniae* (~30% susceptibility; 95% CI: 28.0–32.0%) necessitates pathogen-specific alternatives [18].

Co-trimoxazole's efficacy in *E. coli* increased gradually to 52% by 2022 (95% CI: 50.2–53.8%), supporting its role as a viable alternative for empirical therapy in uncomplicated cases, though its lower susceptibility compared to nitrofurantoin requires careful consideration [17,18]. For *K. pneumoniae*, *co-trimoxazole* susceptibility improved from ~40% in 2014 to 56% in 2022 (slope: +2.0%/year, p=0.02; 95% CI: 53.8–58.2%), contrasting with global trends where resistance often exceeds 70% due to folate pathway gene mutations [13]. Regional variability in South India (36–68% susceptibility) compared to a national average of 49% highlights the need for localized prescribing practices [12,13]. Broader Indian cohorts report higher *co-trimoxazole* resistance (71–83%), particularly in tertiary settings with frequent antibiotic exposure, underscoring the importance of culture-guided therapy to mitigate treatment failures [20]. The uptick in *K. pneumoniae* susceptibility may reflect reduced selective pressure from competing agents like quinolones, warranting further investigation [13].

The significant decline in third-generation cephalosporin susceptibility (from 44% to 30% in *E. coli*; slope: -1.8%/year, p<0.001) and ciprofloxacin susceptibility (from 33% to 18%; slope: -1.9%/year, p<0.001) mirrors national and regional trends, driven by overuse and dissemination of ESBL and quinolone resistance genes [11,16]. Ciprofloxacin resistance, reaching 82% in central Indian communities, reflects rampant over-the-counter antibiotic use and inadequate regulatory oversight, rendering quinolones and cephalosporins unreliable for empirical CA-UTI treatment [16]. ESBL prevalence (30% in *E. coli*, 40% in *K. pneumoniae*) aligns with 2020–2025 Indian data, ranging 16.8–63% for *E. coli* and 37–49% for *K. pneumoniae*, often mediated by plasmid-encoded genes like *bla*CTX-M [14,19,24]. Higher ESBL rates in eastern and western India (up to 63%) compared to lower rates in pediatric populations (21.7–33.2%) suggest regional and demographic variations, possibly linked to differential antibiotic exposure and healthcare access [19,21]. The rise in carbapenem resistance in *K. pneumoniae* (from 10% to 25%; p<0.01) is particularly concerning, signaling a growing threat to last-line therapies in community settings [16].
Enterococcus spp. exhibited high susceptibility to nitrofurantoin, fosfomycin, and teicoplanin (90–100%) and vancomycin (83%), with no vancomycin-resistant isolates, underscoring their utility for gram-positive CA-UTIs, though their low prevalence (3.2%) limits overall impact [18]. The increase in multidrug resistance (MDR) from 25% to 35% (p<0.001) highlights the escalating AMR burden, driven by ESBL and quinolone resistance mechanisms, often plasmid-mediated [14].
This study's strengths include its large sample size (n=5,550) and longitudinal design, providing robust temporal insights that surpass cross-sectional studies [23]. Limitations include potential tertiary-care bias toward resistant strains and the lack of data on comorbidities (e.g., diabetes, immunosuppression) or prior antibiotic exposure, which could influence resistance profiles [23]. Future research should integrate genomic sequencing to elucidate resistance mechanisms (e.g., ESBL or carbapenemase genes) and explore environmental and behavioral factors driving AMR in Southern India [14]. These findings advocate for localized antibiograms, as recommended by the World Health Organization's Global Action Plan on AMR, to guide empirical therapy and strengthen antibiotic stewardship in high-prevalence, resource-limited settings [15].

CONCLUSION

Amid rising AMR, nitrofurantoin and *co-trimoxazole* remain effective empirical therapies for uncomplicated CA-UTIs in Southern India, with nitrofurantoin maintaining high *E. coli* susceptibility and *co-trimoxazole* showing moderate efficacy despite regional variability. For *K. pneumoniae*, alternative agents are needed due to increasing carbapenem resistance. Local antibiograms, aligned with WHO stewardship guidelines, are essential to preserve these drugs, curb MDR, and reduce UTI morbidity in high-prevalence settings. Molecular surveillance offers a pathway for proactive AMR management.

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