

SUSCEPTIBILITY PATTERNS IN GRAM NEGATIVE URINARY ISOLATES TO CIPROFLOXACIN, CO-TRIMOXAZOLE AND NITROFURANTOIN

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ABSTRACT: BACKGROUND: Urinary tract infection (UTI) is one of the commonest infections, requiring antibiotic therapy, encountered in clinical practice. Ciprofloxacin, co-trimoxazole (trimethoprim-sulfamethoxazole) and nitrofurantoin are three of the commonest drug used for the treatment of uncomplicated UTI. In this study, we describe the resistance rates of Gram negative uropathogens to these three antimicrobial agents. **MATERIALS AND METHODS:** This was a retrospective study on bacteria isolated from the urine samples submitted to the department of microbiology based on laboratory data. Among all the patients in whom urine culture was performed in our laboratory from 01.01.2008 to 31.08.2011, those showing significant bacteriuria (more than 1,00,000 colony forming units per ml of urine) with Gram negative bacteria were included in this study. The data on susceptibility of these isolates to ciprofloxacin, co-trimoxazole and nitrofurantoin was then analysed. Results: 1,422 Gram negative bacterial isolates were included in the study. The commonest isolates were: *Escherichia coli* (67.30%), *Klebsiella pneumoniae* (16.03%) and *Pseudomonas aeruginosa* (6.96%). *Escherichia coli* isolates were most susceptible to nitrofurantoin with a susceptibility rate of 95.72%. Isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were most susceptible to ciprofloxacin, with susceptibility rates of 59.21% and 35.35%, respectively. Total susceptibility to nitrofurantoin, co-trimoxazole and ciprofloxacin, among all isolates was 76.02%, 43.95% and 46.13% respectively. **CONCLUSION:** *Escherichia coli* and *Klebsiella* spp. are the commonest isolates encountered in UTIs. As a first-line therapeutic option for uncomplicated lower UTI, nitrofurantoin seems to very effective.

KEY WORDS: Antibiotic susceptibility, *Escherichia coli*, *Klebsiella*, UTI, Urinary tract infection

BACKGROUND: Urinary tract infection (UTI) is one of the commonest infections, warranting antibiotic use, encountered in medical practice, both in the out-patient as well as in the in-patient setting.¹ This infection is far commoner in women: more than 50% have at least one episode of UTI in their lifetime, with a significant proportion of these suffering from at least one recurrence.^{2,3} While less common than in women, UTI in males is often associated with structural and/or functional abnormalities of the urinary tract.⁴

UTI may involve the lower urinary tract, the upper urinary tract, or both. Lower UTI is labelled as cystitis, and presents with symptoms of dysuria, frequency and urgency, often with supra-pubic tenderness. Upper UTI includes pyelonephritis, which presents with flank pain and fever, and is often associated with dysuria, frequency and urgency. These symptoms, however, can occur in the absence of infection as well: a positive urine culture exhibiting significant bacteriuria (more than 1,00,000 colony forming units per ml of urine) is essential to conclusively label these cases as UTI.⁵

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Treatment of uncomplicated UTI is not usually problematic, but alarmingly, in the recent years, the incidence of multi-drug resistant uropathogens has been undergoing a steady and rapid increase.⁶

Ciprofloxacin, co-trimoxazole (trimethoprim-sulfamethoxazole) and nitrofurantoin are three of the commonest drug used for the treatment of uncomplicated lower UTI.⁷ Among these, nitrofurantoin is effective only in cases of lower UTI: as the drug is rapidly excreted in the urine, and serum concentrations never reach therapeutic levels.⁸ On the other hand, both co-trimoxazole and ciprofloxacin are effective in upper and lower UTI caused by susceptible organisms.⁹ In this study, we describe the resistance rates of Gram negative uropathogens to these three antimicrobial agents.

MATERIALS AND METHODS: This was a retrospective study on bacteria isolated from the urine samples submitted to the department of microbiology based on laboratory data. The study was conducted in Sree Gokulam Medical College, a tertiary-care teaching hospital in Trivandrum, Kerala, India.

Among all the patients in whom urine culture was performed in our laboratory from 01.01.2008 to 31.08.2011, those showing significant bacteriuria (more than 1,00,000 colony forming units per ml of urine) with Gram negative bacteria were included in this study. Among these, cases without data on the susceptibility to nitrofurantoin, co-trimoxazole or ciprofloxacin were excluded from the study. However, organisms known to be intrinsically resistant to nitrofurantoin and co-trimoxazole (such as *Pseudomonas aeruginosa*) were included in the study, and were counted as isolates resistant to nitrofurantoin and co-trimoxazole.^{8,9}

As per the above mentioned inclusion and exclusion criteria, a total of 1,442 isolates were included in the study. These organisms had been isolated in culture and identified according to standard microbiological techniques. Antibiotic susceptibility testing had been performed as per the CLSI guidelines which were recommended at that time.¹⁰⁻¹³ This data was extracted from the laboratory database and fed into LibreOffice Calc (version 3.5.7.2). After organising the data in Calc, it was analysed using the statistical software R (version 2.14.1).

RESULTS: As mentioned earlier in this article, 1,422 Gram negative bacterial isolates were included in this study. Among these, 848 (59.63%) were obtained from in-patients, while 574 (40.37%) were obtained from out-patients. The commonest organisms isolated was *Escherichia coli* (957 isolates: 67.30%), *Klebsiella pneumoniae* (228 isolates: 16.03%) and *Pseudomonas aeruginosa* (99 isolates: 6.96%). The details of other isolates are given in Table 1.

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Organisms	IP	OP	Total
Acinetobacter baumannii	35	7	42
Citrobacter freundii	28	19	47
Enterobacter aerogenes	12	6	18
Escherichia coli	537	420	957
Klebsiella oxytoca	4	4	8
Klebsiella pneumonia	138	90	228
Proteus mirabilis	7	5	12
Proteus vulgaris	6	3	9
Pseudomonas aeruginosa	80	19	99
Serratia marcescens	1	1	2
Total	848	574	1422

Table 1: Gram negative bacteria isolated from urine

Among the total isolates, 1,081 (76.02%) isolates were susceptible to nitrofurantoin. However, only 625 (43.95%) and 656 (46.13%) isolates were susceptible to co-trimoxazole and ciprofloxacin, respectively. Not surprisingly, susceptibility rates were higher in isolates from out-patients than in isolates from in-patients (Figure 1).

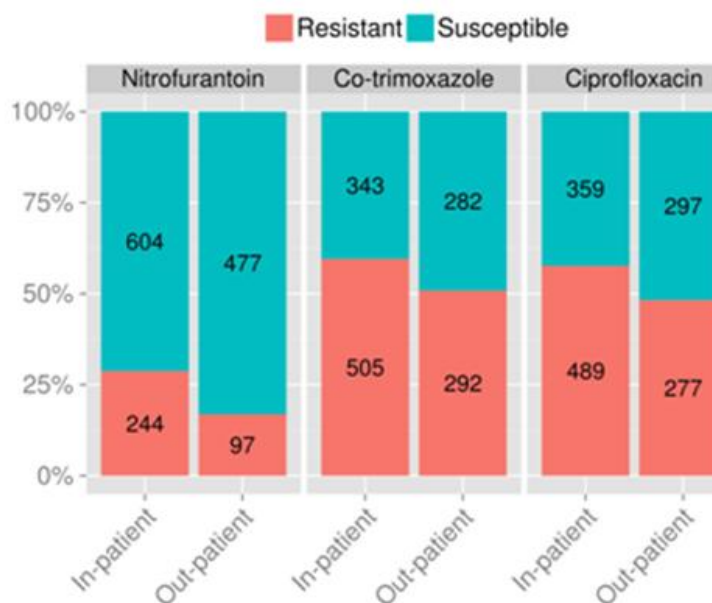


Fig. 1: Overall susceptibility of Gram negative urinary isolates to ciprofloxacin, co-trimoxazole and nitrofurantoin

Among *Escherichia coli* isolates, 916 (95.72%) were susceptible to nitrofurantoin, whereas only 426 (44.51%) and 395 (41.27%) isolates were susceptible to co-trimoxazole and ciprofloxacin, respectively. Among the isolates of *Klebsiella pneumoniae* (the next commonest organism), ciprofloxacin appeared to be the most useful antibiotic, with 135 isolates (59.21%) being

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susceptible. Susceptibility to co-trimoxazole and nitrofurantoin among *Klebsiella pneumoniae* isolates were 51.75% (118 isolates) and 48.25% (110 isolates), respectively. *Pseudomonas aeruginosa* (the third commonest organism isolated) is intrinsically resistant to nitrofurantoin and co-trimoxazole. Ciprofloxacin was, thus, the only useful drug among the three for this organism, with a susceptibility rate of just 35.35% (35 isolates). The details of other isolates are given in Figure 2.

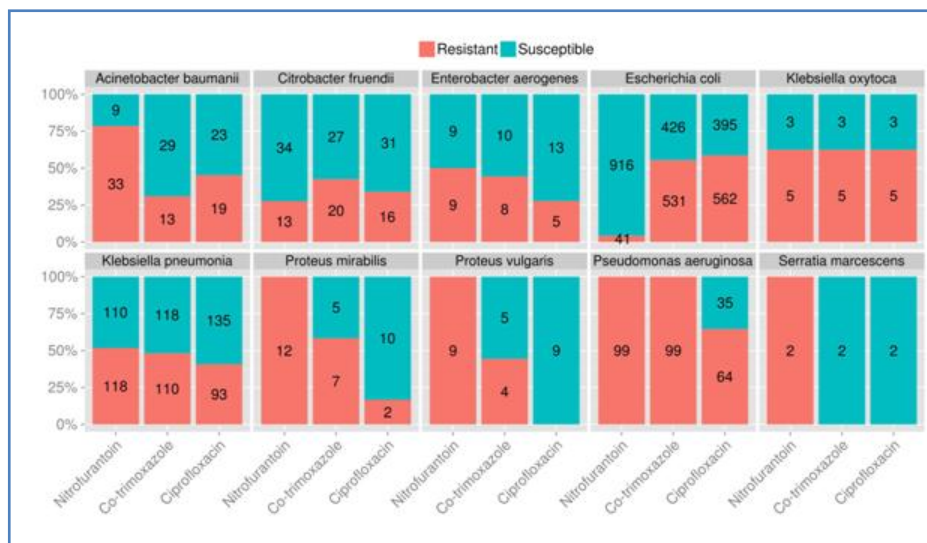


Fig. 2: Antibiotic susceptibility of Gram negative isolates from urine

DISCUSSION: An evaluation of the frequency of occurrence and antimicrobial susceptibility patterns of Gram-negative bacteria isolated from bacteremic patients with UTI from European Union (EU) and United States (USA) hospitals shows that the most frequently isolated pathogens were *Escherichia coli* (63.3/71.3% in USA/EU), *Klebsiella* spp. (16.7/11.2%) and *Proteus mirabilis* (6.4/5.0%).¹⁴ Another study from Korea shows the most common causative microorganisms for UTI were *Escherichia coli* (81.4%), *Klebsiella pneumoniae* (8.4%), *Enterobacter* spp. (1.7%), and *Proteus* spp. (0.4%).¹⁵ Our study too, reflects a similar pattern: the two commonest organisms isolated were *Escherichia coli* (957 isolates: 67.30%) and *Klebsiella pneumoniae* (228 isolates: 16.03%). However, *Pseudomonas aeruginosa* (99 isolates: 6.96%) was the third commonest isolate. Thus, this study exhibits concurrence with global statistics regarding urinary isolates from patients with UTI, especially with respect to *Escherichia coli* and *Klebsiella* spp.

In 2009, the Study for Monitoring Antimicrobial Resistance Trends (SMART) was expanded to include surveillance of Gram-negative pathogens causing UTIs in the Asia-Pacific region. Analysis of isolates were collected from 38 centres in 11 countries from patients with UTIs in 2009 and 2010 shows that 86.0% of the isolates were Enterobacteriaceae, of which *Escherichia coli* (56.5%) and *Klebsiella pneumoniae* (13.8%) were the two most common species. Amikacin was the most effective antibiotic (91.7%), followed by ertapenem (86.9%), imipenem (86.6%), and piperacillin-tazobactam (84.9%). For ciprofloxacin and levofloxacin, the susceptibility rates were 51.4% and 54.4%, respectively¹⁶.

In a study conducted in Western Nepal, *Escherichia coli* was found to be most susceptible to amikacin (98%), followed by gentamicin (87.9%), ceftazidime (80.8%), amikacin (87.2%),

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ciprofloxacin (74.8%), norfloxacin (78.4%) and co-trimoxazole (77.9%).¹⁷ In this study, 95.72% of *Escherichia coli* isolates were susceptible to nitrofurantoin, whereas only 44.51% and 41.27% of the isolates were susceptible to co-trimoxazole and ciprofloxacin, respectively.

CONCLUSION: The commonest organism causing urinary tract infection is still *Escherichia coli* and majority are sensitive to nitrofurantoin. *Klebsiella* spp, the next commonest urinary isolate, is most sensitive for ciprofloxacin. As a first-line therapeutic option for uncomplicated lower UTI, nitrofurantoin seems to very effective.

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