

Prevalence of Antibiotic Resistance among Patients with Escherichia Coli Urinary Tract Infection in a Private Hospital at Lahore-Pakistan

SIDRA CHEEMA¹, SHAFIQ UR REHMAN CHEEMA²

ABSTRACT

Of 127 urine isolates from patients at national hospital and medical center 93 were positive for Escherichia Coli (E.Coli). Out of these 93 isolates, 73%, 77%, 82% & 71% were resistant to fluoroquinolones, trimethoprim-sulfamethoxazole (SXT), Ampicillin-sulbactam & Ceftriaxone respectively. Resistance to Nitrofurantoin, Fosfomycin, Piperacillin-Tazobactam, Cefoperazone-Sulbactam & Carbapenems (Imipenem-Cilastatin, Meropenem) was found to be only 14%,8.7%,4.4%,1.4% & 1.1% respectively. For uncomplicated urinary tract infection (UTI) empiric antibiotics should include Nitrofurantoin and Fosfomycin. For severe and complicated infection parenteral antimicrobial with least resistance should be used.

Keywords: Escherichia Coli, UTI, bacterial resistance, fluoroquinolones resistant

INTRODUCTION

There are an estimated 150 million urinary tract infections per annum worldwide¹. Urinary tract infections are the most common bacterial infections in women and account for significant morbidity and health care costs^{1,2}. Among both outpatients and inpatients, Escherichia coli is the primary urinary tract pathogen, accounting for 75 to 90% of uncomplicated urinary tract infection isolates^{2,3}.

Infectious Disease Society of America recommends that physicians obtain information on local resistance rates and that ongoing surveillance be conducted to monitor changes in susceptibility of uropathogens. It also recommends that alternative therapy for uncomplicated UTIs in the setting with > 10 to 20% SXT resistance may include a beta lactam, fluoroquinolones, Nitrofurantoin or Fosfomycin. Fluoroquinolones, in particular ciprofloxacin, are used increasingly but resistance to ciprofloxacin is also increasing. The widespread use of fluoroquinolones for such a common infection raises concerns regarding the possibility of accelerated development of resistance⁴.

UTI is the most common disease effecting urinary tract and it is major cause of morbidity. Fluoroquinolones and beta lactam antibiotics are commonly prescribed for patients with signs and symptoms consistent with uncomplicated urinary tract infection. We noticed that poor response to empiric antimicrobial at our institution and wanted to test the hypothesis that this probably is secondary to

increasing resistance to commonly prescribed antibiotics

The aim of this study was to assess the prevalence of antimicrobial resistance and determine appropriate empiric antibiotic therapy among patients with urinary tract infection secondary to *E. coli*.

PATIENTS AND METHODS

This cross-sectional study was carried out at the clinical pathology laboratory of National Hospital & Medical Center, Lahore, Pakistan between July 1, 2014 to June 30, 2015 for a period of one year. A total of 123 urine isolates from inpatient and outpatient were received. These patients were suffering from UTI and confirmation was made from their clinical records. Only 93/123 positive E.Coli cultures were included for further analysis of susceptibility and resistance patterns. Then medical records of these patients were reviewed for the following variables: age, sex, type of isolate on urine culture, sensitivity and resistance pattern to different antimicrobials and ESBL status. No patient with positive E.Coli in urine culture was excluded based on first or subsequent, lower or upper and complicated or uncomplicated UTIs.

RESULTS

Of 127 patients urine isolates 93 were positive for E.Coli. The mean age was 52 (range= 1-93, median 63). There were 30%(28/93) men and 70% (65/93) women. Out of these 93 urine isolates, 73%,77%,82% & 71% were resistant to fluoroquinolones, trimethoprim-sulfamethoxazole, Ampicillin-sulbactam & Ceftriaxone respectively. Resistance to Nitrofurantoin, Fosfomycin, piperacillin-tazobactam, Cefoperazone-Sulbactam & carbapenems

¹Assistant Professor Pathology, CMH Lahore Medical College

²Assistant Professor of Nephrology, CMH Lahore Medical College
Correspondence to Dr. Shafiq ur Rehman Cheema,
Email: shafiqcheema@yahoo.com Cell: 0311-238-1111

(Imipenem-Cilastatin, Meropenem) was found to be only 14%,8.7%,4.4%,1.4% & 1.1% respectively

In terms of ESBL producing organism,46% (43/93)were positive for ESBL and 54% (50/93) were negative for ESBL. All ESBL producing bacteria were resistant to ampicillin and Ceftriaxone but among ESBL negative, only 11/50 (22%) & 16/50 (32%) were sensitive to amoxicillin/ampicillin and Ceftriaxone respectively indicating prevalence of high resistance to these beta lactam. Women found to be

more sensitive to Quinolones & fluoroquinolones as compared to men. Sensitivity of patients age less than 30 years was not much different from overall sensitivities except for Quinolones & fluoroquinolones. E coli appeared to be more sensitive to Quinolones & fluoroquinolones for younger patients. The following table shows the results of sensitivities & resistance pattern of E.Coli to commonly prescribed antimicrobial used in clinical practice..

Table

Antibiotic	Overall sensitivity	Overall Resistance	Sensitivity ESBL(+)	Sensitivity ESBL(-)	Sensitivity Women	Sensitivity Men	Sensitivity age<30
TMP-SXT	22.5	77.5	16.2	24	21.1	25	32.1
Quinolones	15	85	2.3	26	18.4	7.1	32.1
Fluoroquinolones	26.8	73.2	20.9	34	30.7	17.8	35.7
Amoxil/Ampicillin	17.2	82.8	0.0	22	10.7	17.8	17.9
Ceftriaxone	29	71	2.3	32	20	17.8	17.9
Aztreonam	34.4	65.6	32.5	38	32.2	39.2	35.7
Fosfomycin	91.3	8.7	83.7	94	78.4	85.7	89.2
Nitofurontoin	86	14	81.3	86	84.6	85.7	85.7
Piperacillin-Tazobactam	97.8	2.2	93	98	96.9	96.4	100
Cefoperazone-Sulbactam	95.6	4.4	90.6	100	95.3	96.4	100
Carbapenems	98.9	1.4	95.3	100	98.4	96.4	100

DISCUSSION

The microbial spectrum of uncomplicated cystitis and Pyelonephritis consists mainly of *Escherichia coli* (75 to 95 percent), with occasional other species of Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and other bacteria such as *Staphylococcus saprophyticus*^{5,6}. Other gram-negative and gram-positive species are rarely isolated in uncomplicated UTIs. Therefore, local antimicrobial susceptibility patterns of *E. coli* in particular should be considered in empiric antimicrobial selection for uncomplicated UTIs.

The rate of resistance to fluoroquinolones (like ciprofloxacin), beta lactam (like ampicillin and Ceftriaxone) and TMP-SXT were concerning, as fluoroquinolones are now the most commonly prescribed therapy for UTI^{7,8}.

Extended-spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. Infections with ESBL-producing organisms have been associated with poor outcomes. Community and hospital-acquired ESBL-producing Enterobacteriaceae are prevalent worldwide⁹.

The resistance to Fosfomycin and Nitofurontoin was found to be low, suggesting that these agents should be strongly considered as a first-line empirical treatment for uncomplicated lower UTIs. In another study in young college women, there was not a single

case of resistance to Nitofurontoin making it first line therapy¹⁰.

In USA because of low resistance to fluoroquinolones, for outpatient treatment of uncomplicated Pyelonephritis we suggest ciprofloxacin (500 mg orally twice daily for seven days or 1000 mg extended release once daily for seven days) or levofloxacin (750 mg orally once daily for five to seven days) is recommended but given high resistance in our study we recommend alternatives like parenteral antimicrobial agents like piperacillin-tazobactam, Cefoperazone-Sulbactam and carbapenems should be used.

Considerations in selecting an agent for treatment of acute cystitis include efficacy, risk of adverse effects, resistance rates, propensity to cause ecological adverse effects of antimicrobial therapy (such as selection of drug-resistant organisms and development of colonization or infection with multidrug-resistant organisms), cost, and drug availability¹¹. None of the antimicrobials currently available clearly outweighs the others in terms of optimizing each of these factors for treatment of acute cystitis, and the optimal antimicrobial in one region may be different from that in another.

Appropriate antimicrobials for treatment of acute uncomplicated cystitis in women include Nitrofurantoin monohydrate (100 mg orally twice daily for 5 days); early clinical efficacy rate with 5 to 7 day regimen 90 to 95 percent based on randomized trials

(11-15) and minimal resistance and ecological adverse effects. Nitrofurantoin should be avoided if there is suspicion for early pyelonephritis, and is contraindicated when creatinine clearance is <60. Trimethoprim-sulfamethoxazole Empiric TMP-SMX should be avoided if the prevalence of resistance is known to exceed 20 percent^{16,17} so based on the results of our study we should avoid this.

Fosfomycin (3 grams single dose)¹⁴; clinical efficacy rate 91% from one randomized trial¹⁴ but bacterial efficacy inferior compared with other first-line agents minimal resistance and ecological adverse effects. Fosfomycin should be avoided if there is suspicion for early pyelonephritis. In our study sensitivity to Fosfomycin was also 91.7% for e coli isolates so it is a good choice for uncomplicated cystitis. These antibiotic options and suggested treatment durations for acute uncomplicated cystitis are the same for any adult woman with acute uncomplicated cystitis, regardless of age. A systematic review of studies evaluating treatment of cystitis in community-dwelling adults ≥65 years of age concluded that the optimal regimens are the same as those recommended for younger adults and that shorter antibiotic courses (3 to 6 days) resulted in similar outcomes as longer ones (7 to 14 days)¹⁸.

Acceptable beta lactam agents include amoxicillin-clavulanate, cefpodoxime, cefdinir and cefaclor, for duration of seven days^{18,19,20}. Cefpodoxime (three-day regimen) did not meet criteria for noninferiority to ciprofloxacin (three-day regimen) for clinical cure of acute uncomplicated cystitis in a randomized trial²¹. Other beta lactams, such as cephalixin, are less well studied but may be acceptable in certain settings. Ampicillin or amoxicillin should not be used for empiric treatment given poor efficacy and high prevalence of resistance to these agents²²⁻²⁷. In our study we also found very high resistance to these beta lactam antibiotics and we don't recommend the empiric use of these antibiotics.

Pyelonephritis, on the other hand, is a more serious infection than cystitis; therefore, expected efficacy of an antimicrobial agent is of greater importance than concern about ecological adverse effects¹¹.

For outpatients with mild to moderate Pyelonephritis in whom the likelihood of fluoroquinolones resistance is expected to be less than 10, it has been suggested to use a fluoroquinolones for empiric therapy²⁸⁻³² but since in our study population the prevalence of resistance is much higher we don't recommend fluoroquinolones for empiric use for outpatient treatment of Pyelonephritis. In this setting of fluoroquinolones resistance, other acceptable choices based on susceptibility data should be considered. Use of Nitrofurantoin and fosfomycin, should be avoided in

the setting of pyelonephritis because they do not achieve adequate renal tissue levels¹¹.

For inpatient with pyelonephritis requiring hospitalization should be treated initially with an intravenous antimicrobial regimen such as a fluoroquinolones, an aminoglycoside (with or without ampicillin), an extended-spectrum cephalosporin, an extended-spectrum penicillin, or a carbapenem²⁴. The choice between these agents should be based on local resistance data and tailored on the basis of susceptibility results.

Pyelonephritis caused by extended-spectrum beta-lactamase (ESBL)-producing strains should be treated with a carbapenems^{33,34}. Empiric antibacterial coverage for ESBL-producing organisms is warranted for patients presenting with sepsis involving the urinary tract³³.

Population-based studies have documented increasing resistance of *E. coli* urinary isolates to fluoroquinolones and trimethoprim-sulfamethoxazole; some studies have suggested that resistance has increased in particular among elderly patients³⁵. Strains that produce extended-spectrum beta-lactamases (ESBL) are also increasing in frequency. Nitrofurantoin and Fosfomycin are active in vitro against ESBL producing strains (36-38) In a case-control study including 113 patients with ESBL-producing *E. coli* UTIs, no resistance to fosfomycin was detected and clinical cure rates were high (93 percent)³⁹. In the US, resistance to all oral options is still uncommon among outpatients with *E. coli* cystitis. In such cases, a carbapenem is the best option (e.g., Ertapenem once daily either IV or .IM.) When parenteral antibiotics are indicated, any choice with low resistance and high susceptibility like piperacillin-tazobactam, Cefoperazone-Sulbactam and carbapenems should be used.

The study likely overestimates the prevalence of antibiotic resistance in *E. coli*, as patients who responded empirical therapy, and presumably had susceptible organism, would not have had urine culture and sensitivity tests performed and would not have been included in the study.

CONCLUSION

Fluoroquinolones and beta lactam resistance was found to be very high. There was little resistance to Nitrofurantoin and fosfomycin, carbapenems, piperacillin-tazobactam, and Cefoperazone-Sulbactam. Extended spectrum beta lactamase (ESBL) production confer higher resistance especially to beta lactam antimicrobials without a beta lactam inhibitor. For treatment of acute uncomplicated cystitis, we suggest to use Nitrofurantoin or Fosfomycin. Pyelonephritis requiring hospitalization should be treated initially with an

intravenous antimicrobial regimen such as an extended-spectrum cephalosporin like Cefoperazone-Sulbactam, extended-spectrum penicillin like piperacillin-tazobactam, or a carbapenems like Imipenem-Cilastatin or Meropenem.

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