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Risk factors associated with trimethoprim-sulfomethoxazole among Escherichia coli strains isolated from community acquired urinary tract infection

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Running title: urinary tract infection

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Abstract

Urinary tract infections (UTIs) are common infections affecting all age groups particularly adults. The present study was carried out to determine the risk factors for trimethoprim – sulfamethaxoazole (TMP-SMX) and ciprofloxacin-resistant Escherichia coli (E.coli) isolates obtained from community-acquired UTI. For the study, a total of 595 patients aged between 15 and 70 years with community-acquired UTI were prospectively recruited; 492 (82.69%) of these samples were sterile. Of the 93 Gram-negative isolates included in this study, 56 and 37 isolates were obtained from uncomplicated and complicated UTI, respectively. Since all the male patients were categorized in the complicated UTI group, all 56 non-complicated cases were female patients and 61 (84.72%) of the complicated cases were female patients. The median age was 55 (SD 15.7) and 49 (SD 16) for the uncomplicated and the complicated UTI patients, respectively. 30.36% and 86.49% of uncomplicated and complicated UTI patients were from a rural area. E. coli was the causative agent in 83.93% and 67.57% in the uncomplicated and complicated UTI, respectively (P < 0.0174). Nitrofurantoin and fosfomycin were having the resistance rates of 3.57% and 1.18%, respectively for uncomplicated UTI strains. ESBL were detected in 3.6% and 5.66% of the E. coli strains isolated from uncomplicated and complicated UTIs, respectively. In summary, TMP/SMX may not be appropriate for the empirical treatment of community-acquired UTI due to its widespread resistance. However, ciprofloxacin may be used warily for both uncomplicated and complicated UTI because of emerging resistance.

Running title: urinary tract infection

Key words; ciprofloxacin resistance, trimethoprim-sulfomathoxazole resistance, community acquired urinary tract infection

Introduction

Urinary tract infections (UTIs) are common infections affecting all age groups particularly elderly populations[1]. The treatment modalities of UTI depends on various factors such as age of the patient, sex , underlying disease, infecting agent and the site of involvement of the urinary tract such as upper or lower tract[2]. Further, urine culture is continues to be the authoritative method to diagnose infection in this population and the Escherichia coli (E.coli) continues to be the predominant etiology of UTI[1,3].

UTI may be community acquired or hospital acquired (4). In case of community acquired UTI , trimethoprim-sulfomethoxazole (TMP-SMX), ciprofloxacin, cephalosporins, semi-synthetic penicillins with or without inhibitors, nitrofurantoin and fosfomycin are the most commonly used antibacterial drugs in the treatment[5]. However, due to the increasing frequency of drug resistant strains of uropathogens , the effectiveness of commonly used standard antibiotic regimens are decreasing[3]. Infectious Diseases Society of America (IDSA) recommends, TMP/SMX to treat UTI in settings with low prevalence of drug resistant strains (<10–20%).However, Fluoroquinolones are indicated if the TMP/SMX resistance rate is higher than 20 %[2]. In the last two decades, the Fluoroquinolones have been used for community-acquired UTIs and an association between the increase in quinolone prescriptions and an increase in bacterial resistance has been reported from various countries[6-8]. Therefore, therapeutic alternatives in the setting of high resistance against both TMP/SMX and quinolones need to be studied. The current study was designed to determine the various risk factors associated with TMP/SMX and ciprofloxacin resistance of uropathogenic E. coli strains isolated from patients suspected to be having community acquired UTI

Material and methods

Study setting and duration

This prospective observational study was conducted in the department of microbiology, M.M.I.M.S.R., Mullana (Ambala) tertiary care hospital (750 bedded) , over a period of March 2014 to October 2014. This study was approved by the M.M.I.M.S.R, Mullana Ethical committees and informed consent was obtained from the patients.

Study population

Patients aged between 15 and 70 years with community-acquired UTI were prospectively recruited for the study. Male patients, who had more than three episodes of UTI in the last year, those with upper UTI, pregnant patients, patients with urinary tract abnormalities, patients with a urinary catheter, those who had a urological operation, and those who had urolithiasis were interpreted as having complicated UTI. However, patients with history of hospital stay in the last month were the excluded. A pre tested questionnaire was collected from all the patents regarding the demographic characteristics such as age, sex, address, symptoms (like dysuria, urgency, pollakuria) , criteria indicating the presence of complicated UTI, history of hospital stay within the last month, and antibiotic usage within the last year

Specimen collection and processing

Clean-catch midstream urine samples was collected from each patients and inoculated on Cystiene lactose electrolyte deficient media (CLED) using 4 mm calibrated loop specifically; a semi-quantitative technique was used[9]. Pyuria was detected if 5–10 leucocytes in the centrifuged (at 2000 rpm for 5 min) urine. Culture plates were incubated for 18–24 h at 37° C

Identification of bacterial isolates and Antibiotic sensitivity testing

After incubation, the growth was identified by colony characteristics and standard biochemical tests[9]. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method as per the CLSI recommendations with few modifications[10]; antimicrobial susceptibility testing was performed by a disc diffusion method using two panels of antibiotics; one tested against strains from uncomplicated UTI, the other tested against strains from complicated UTI. The antibiotics tested against both groups were ampicillin, amoxicillin/ clavulanate, cefazolin, cefuroxime, ceftriaxone, cefixime, aztreonam,gentamicin, ciprofloxacin, ofloxacin, nalidixic acid, TMP-SMXand sulfisoxazole. In cases of uncomplicated UTI cefadroxil, nitrofurantoin and fosfomycin were tested. However, in complicated UTI; piperacillin, piperacillin/tazobactam, ticarcillin/ clavulanate, cefepime, cefoperazone, ceftazidime and amikacin were tested.

All the Gram-negative bacteria isolated from these clinical samples were tested for ESBL production using four disks (concentration in µg) ceftazidime (30), ceftazidime/clavulanic acid (30/ 10), cefotaxime (30), and cefotaxime/clavulanic acid (30/10) and interpreted as per CLSI guidelines[10].

Quality control

Every new batch of culture media was incubated at 37^0C for overnight to ensure the sterility Quality was assured by testing E. coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 in every batch. However, a non-ESBL producing organism E.coli ATCC 25922 and an ESBL-producing organism K. pneumoniae ATCC 700603 was used while testing ESBL screening and phenotypic confirmatory tests.

Statistical analysis

Data were analyzed using Microsoft Excel (version 2007) and Graph pad prism statistical software (online version). Comparisons for categorical variables were done using Fisher's exact test. Significance was set at $P < 0.05$ using two sided comparisons.

Results

A total of 595 urine samples from outpatients aged between 18 and 70 years were submitted to the microbiology laboratory M.M.I.M.S.R., Mullana during the study period (March 2014 to October 2014); 492 (82.69%) of these samples were sterile. Patients who had urinary tract infection symptoms and $>10^5$ Gram-negative bacterial growth in the urine were included in this study. Of the 93 Gram-negative isolates included in this study, 56 were isolated from uncomplicated UTI and 37 were isolated from complicated UTI. As male patients were categorized in the complicated UTI group, all 56 uncomplicated cases were female patients and 61 (84.72%) of the complicated cases were female patients. The median age was 55 (SD 15.7) for the uncomplicated UTI patients and 49 (SD 16) for the complicated UTI patients. Seventeen (30.36%) of 56 uncomplicated UTI patients and 32 (86.49%) of 37 complicated UTI patients were from a rural area. E. coli was the causative agent in 83.93% of the uncomplicated UTIs and 67.57% in complicated UTI ($P < 0.0174$) (Table 1). Table 2 shows antibitotic reistance pattern of E. coli isolates obtained from community acquired UTI. Nitrofurantoin and fosfomycin had the resistance rates 3.57% and 1.18%, respectively for uncomplicated UTI strains. ESBL were detected in 3.6% and 5.66% of the E. coli strains isolated

from uncomplicated UTI and complicated UTI, respectively.

Table 3 depicts risk factors for ciprofloxacin resistance among E coli strains isolated. On analysis of the data for risk factors for ciprofloxacin resistance among E coli strains (Table 3), age over 46 ($P < 0.0038$), isolates from a rural area ($P < 0.0102$), complicated UTI ($P < 0.0001$), ESBL production ($P < 0.001$) and ciprofloxacin use were found to be significantly associated with ciprofloxacin resistance among E. coli strains. Receiving ciprofloxacin more than once in the last year was significantly associated with ciprofloxacin resistance (P 0.0001) whereas other antibiotic regimens were not ($P > 0.135$).

Table 4 demonstrates risk factors for TMP/SMX resistance among E coli strains isolated. On univariate analysis, the risk factors for TMP/SMX resistance among E coli strains (Table 4), age over 46 ($P < 0.0475$), isolates from a rural area ($P < 0.002$), complicated UTI ($P < 0.0003$), ESBL production ($P < 0.10$) and TMP/SMX use were found to be significantly associated with TMP/SMX resistance among E. coli strains. Receiving TMP/SMX more than once in the last year was significantly associated with TMP/SMX resistance ($P < 0.0212$) whereas other antibiotic regimens were not ($P > 0.1369$).

Discussion

Empirical antibiotic treatments are indicated in conditions where the community acquired UTIs are diagnosed. However, the increasing incidence of antibiotic resistant bacterial infections makes empirical treatments more intricate[11]. Therefore, it is essential to understand the local antibiotic susceptibility patterns for the prescription of the appropriate antibiotics. The current study was designed to establish the antibiotic susceptibility patterns of E. coli strains isolated from community acquired UTIs and to describe the risk

factors imparting to the resistance. The current study explores that the E coli continues to be the most frequent pathogen in both community acquired uncomplicated (83.93%) and complicated UTI (67.57%). This higher frequency of E. coli UTI could be attributed to the ability of these strains to ascend up from the perianal area (in female patients) into the urinary tract due to its close proximity. Further, the percentage of distribution of E. coli obtained in the current study was consistent with previous reports as well[12].

In general, the antimicrobial resistance rates of E. coli strains isolated from complicated UTI are higher than the uncomplicated UTI E.coli strains.[5,13]. In the current study, table 2 demonstrates the persistence of higher antimicrobial resistance among E. coli strains isolated from community acquired complicated UTI. This higher resistance among the E. coli strains (isolated from complicated UTI) may be due to the transfer of drug resistant genes (either plasmid or chromosomally mediated) from the drug resistant bugs prevailing in the community. Further, the distribution of antimicrobial resistant strains were in accordance with the earlier studies as well[5,13].

In community acquired UTI, the TMP/SMX and ciprofloxacin are recommended for treatment[6]. IDSA also recommends the use of TMP/SMX as a drug choice for uncomplicated UTI. However, in the current study 37.93% of the uncomplicated strains and 62.07% of the complicated strains were resistant to TMP/SMX. This higher TMP/SMX rates were also reported from earlier studies as well[8,14]. However, the exact causes of high TMP-SMX resistance were not explored. But investigators suggest that this higher resistance could be due to the irrational prescription and extensive usage of TMP/SMX in the community[11,15].

IDSA recommends, TMP/SMX to treat UTI in settings with low prevalence of drug resistant strains (<10–20%)[2]. Further, TMP/SMX may also be used for the empirical treatment of UTIs in the age group of 20–64 years of female patients and in the age group 0–6 years of male patients, wherein the resistance rates were low[15]. However, fluoroquinolones are indicated when the TMP/SMX resistance rate is higher than 20%[2]. In the current study, the resistance to ciprofloxacin is of great concern because fluoroquinolones are used as rational empirical agents for the treatment of both uncomplicated and complicated UTI in areas where resistance to TMP/SMX is over 20%[7,16]. In the current study, ciprofloxacin resistance was found to be 36.36% in complicated UTI and 63.64% in uncomplicated UTI and this data was comparable with previous reports as well[12]. This higher resistance rate could be due to the irrational and extensive use of ciprofloxacin since it is considered as drug of choice in UTI where the TMP/SMX resistance is common. Further, the univariate analysis indicated that age over 46, ciprofloxacin use and complicated UTI were independent risk factors contributing to ciprofloxacin resistance (Table 3). The association between ciprofloxacin use and the emergence of resistance has been reported previously also[7, 13, 14, 17, 18]. Similarly, complicated UTI (including male gender), urinary tract abnormalities, urinary catheterization and older age were found to be associated with high ciprofloxacin resistance rates in previous studies. This outcome was consistent with the current study as well.[13, 17, and 18]. Further, it is evident from the table 3 ad 4 that the frequency of ESBL production was more common among ciprofloxacin resistant uropathogenic E. coli isolates ($P < 0.001$) as reported by Tolun et al[19].

Generally, community acquired UTI is treated using TMP/SMX and ciprofloxacin or higher generation beta lactam group of antibiotics. However, nitrofurantoin and fosfomycin may also be used as reasonable alternatives for the treatment of uncomplicated UTI [12]. In the current study, nitrofurantoin and fosfomycin reistance was found to be 3.57% and 1.79% respectively, indicating the potential to treat uncomplicated UTI. Further, nitrofurantoin is recommended for treating uncomplicated cystitis since its resistance to E. coli has been reported to be very low even after 50 years of use[16]. Similarly, the use of fosfomycin is also limited to the treatment of uncomplicated cystitis with the advantage of single dose[20]. However, due to the low level resistance of nitrofurantoin and fosfomycin among E coli isolates obtained from uncomplicated UTI ,suggests that these antimicrobial agents may be investigated for treating complicated UTI as well.

In nutshell, TMP/SMX may not be appropriate for the empirical treatment of community-acquired UTI, due to its widespread resistance. However, ciprofloxacin may be used warily for both uncomplicated and complicated UTI because of emerging resistance. Further, the study recommends the practice of routine urine culture and antibiotic susceptibility in the current study set up. The study also implies the use of nitrofurantoin and fosfomycin as alternatives for the treatment of uncomplicated UTI. However, the use of nitrofurantoin and fosfomycin should also be investigated for its clinical efficacy to use in the treatment of complicated UTI.

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