Antimicrobial Resistance Patterns Amid Community-Acquired Uropathogens in Outpatient Settings of a Tertiary Care Hospital in Thailand

Tharntip Sangsuwan, M.D., Khongkrit Jariyasoonthornkit, M.D., Silom Jamulitrat, M.D.

Department of Family Medicine and Preventive Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, 90110, Thailand.

ABSTRACT

Objective: To document the distribution of antimicrobial resistance patterns of community-acquired uropathogens. Materials and Methods: Outpatient microbiology data of urine culture results in Songklanagarind Hospital between January to December 2019 were reviewed.

Results: This study included 649 episodes of positive urine cultures in 598 patients, in which 80.7% were symptomatic cases. The elderly (median 63 ± IQR 26 years) showed high prevalence of urinary tract infections in this study, for which nearly 80% of all samples were female. The three most common uropathogens identified were: *Escherichia coli (E. coli)* (69.6%), *Klebsiella pneumoniae* (9.5%) and *Staphylococcus saprophyticus* (4.9%). *E. coli* were highly resistant to ciprofloxacin (49.0 %), cotrimoxazole (41.2%) and ceftriaxone (20.6%), but had a low level of resistance to fosfomycin (0%), and amikacin (0.4%).

Conclusion: The antimicrobial resistance pattern of *E. coli* was high for commonly antimicrobial agents used in outpatients; especially quinolone, cotrimoxazole and cephalosporin. However, due to low resistance levels, fosfomycin and amikacin could be considered as effective treatment options for community acquired UTIs in our study.

Keywords: Community; urinary tract infection; antibiotic resistance (Siriraj Med J 2021; 73: 501-509)

INTRODUCTION

Urinary tract infections (UTIs) are amongst one of the common infectious conditions in a primary setting.[1] The main cause of an UTI is bacterial infection, for which 95% of UTI cases, in primary settings, prescribe antibiotics.[2] Frequently, the therapy for an UTI are initiated empirically before the results of urine culture and antibiotic susceptibilities are received. Consequently, drug-resistance may increase, because of frequent and inappropriate use of antibiotics.

The Trend of antibiotic resistance is increasing around the world, with misuse or overuse of antibiotics seemingly being the primary driver of this problem.[3]

In a previous study in Songklanagarind Hospital, 20084, *Escherichia coli (E. coli)* isolated from outpatients with UTIs were resistant to norfloxacin (41.2%), ceftriaxone (16.4%), and cotrimoxazole (49.3%).[4] However, resistance patterns are ever changing over time, and vary in different regions. Therefore, it is necessary to periodically review these changes, for enabling better decision making in antimicrobial selection.

MATERIALS AND METHODS

Setting

We conducted a retrospective cohort study in Songklanagarind Hospital, which is an 860-bed tertiary

Corresponding author: Tharntip Sangsuwan
E-mail: be_med29@hotmail.com
Received 30 June 2021 Revised 15 July 2021 Accepted 16 July 2021
ORCID ID: https://orcid.org/0000-0002-7386-0795
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care facility, serving as a medical school with residency training and as a referral center for the South of Thailand.

Inclusion criteria

- Patients above the age of 15 years who visited the Outpatient Department (OPD) and Emergency Department (ED) from 1 January 2019 to 31 December 2019.
- Single bacterial species with significant bacteriuria ($\geq 10^5$ cfu/ml).
- A clean catch mid-stream urine sample.

Exclusion criteria

- Patients with suspected healthcare issues associated with UTIs; following the adapted Friedman criteria[5], were excluded.

(a) An indwelling urinary catheter in place at the time or within 48 hours before urine collection.

(b) Prior hospital admissions within 90 days.

(c) Regular dialysis or received intravenous chemotherapy within 30 days.

(d) Receiving intravenous therapy, wound care, or nursing care at home within 30 days.

(e) Receiving any urinary procedure within 30 days.

- Patients with follow up clinical symptoms after treatment, and repeat urine cultures.

All positive aerobic urine cultures were identified by the Hospital Information System (HIS). In total there were 1,013 samples from patients presenting with significantly positive urine cultures at the OPD and ED. From this 295 samples were excluded, due to suspected healthcare associated UTI, and 69 samples were excluded due to repeat or follow up urine cultures in the same conditions. Finally, there were 649 samples analyzed in this study.

Definitions

Uncomplicated UTI is identified as a UTI with no relevant functional or anatomical anomalies in the urinary tract or comorbiditie.[6] Complicated UTI is identified as a UTI with one of the following characteristics: male gender, pregnancy, diabetes mellitus, abnormal urological structure, and immunosuppression.[6]

Extended spectrum beta-lactamases (ESBLs) are defined as enzymes produced by certain bacteria that are able to hydrolyze extended spectrum cephalosporin.[7]

Data collection:

Clinical information was extracted from medical databases; including: patient age, gender, medical condition, clinical symptoms of urinary tract infection, risk factors of complicated UTIs, the uropathogens isolate and antibiotic susceptibility. The data was collected via Google form and entered into Microsoft Excel for analysis.

Microbiological studies

Urine collection and processing

Clean-catch midstream urine specimens were processed within 2 hours after collection. In the laboratory, the sample is plated on Mac Conkey medium and Blood agar, by using a standard loop (0.001-millimeter diameter loop). The cultures plated were incubated at 35 ± 2 C, for 18-24 hours. For this study, significant bacteriuria was identified as a culture of a single bacterial species with colony count $\geq 10^5$ cfu/ml. The uropathogens isolated were identified by standard biomedical methods, and susceptibility tests were interpreted corresponding to the Clinical and Laboratory Standard Institute 2019 (CLSI).[8]

Susceptibility testing

The antibiotic discs used were for amikacin, cefotaxime, ceftazidime, cefuroxime, cotrimoxazole, imipenem, tazocin, ampicillin, cefoxtin, ceftriaxone, cephalothin, gentamicin, norfloxacin and meropenem. Extended-spectrum β-lactamases (ESBLs) were interpreted by using zone diameter breakpoints. The CLSI interpretation breakpoint for fosfomycin sensitivity is at least 16 mm, intermediate is between 13-15 mm and resistant is at most 14 mm. Disc diffusion is required for fosfomycin Antimicrobial Susceptibility Testing (AST), and was performed according to the CLSI recommendations.[8]

Data analysis:

Descriptive statistical analysis was performed using Microsoft Excel 2010. Discrete variables were expressed as percentages and proportions. The 95% confidence interval was derived from exact binomial statistic calculation.

RESULTS

All positive aerobic urine cultures were identified by HIS, with 1,013 samples from patients presenting with a significantly positive urine. From this 295 samples were excluded due to suspected healthcare associated UTIs; additionally, 69 samples were excluded due to repeat or follow up urine cultures. Finally, there were 649 samples analyzed in this study.

Sample characteristics

This included; 125 (19.3%) asymptomatic bacteriuria and 524 (80.7%) symptomatic UTIs. Among the symptomatic cases, which were classified to be complicated UTI (57.4%) and uncomplicated UTI (42.6%). (Table 1)

TABLE 1. Demographic data of patients presenting with culture-positive urine in the study.

Variable	N (%)		
	Total N = 649	Asymptomatic bacteriuria N = 125	Symptomatic UTI N = 524
Sex			
Female	512 (79%)	91 (72.8%)	421 (80.3%)
Male	137 (21%)	34 (27.2%)	103 (19.7%)
Age			
Overall Age, Years (Median ± IQR)	63 ± 26	68 ± 22	62 ± 25
15- 30	64 (9.9%)	7 (5.6%)	64 (12.2%)
31 – 45	59 (9.1%)	10 (8%)	59 (11.3%)
46 -60	125 (19.3%)	26 (20.8%)	125 (23.9%)
>60	401 (61.8%)	82 (65.6%)	276 (52.7%)
Medical conditions			
Diabetes mellitus	183 (28%)	48 (38.4%)	135 (25.8%)
Hypertension	222 (34%)	48 (38.4%)	174 (33.5%)
Asthma	18 (3%)	2 (1.6%)	16 (3.1%)
COPD	9 (1%)	0 (0%)	9 (1.7%)
Ischemic heart disease	37 (6%)	6 (4.8%)	31 (5.9)
Thyroid disease	28 (4%)	7 (5.6%)	21 (4%)
Gout	19 (3%)	6 (4.8%)	13 (2.5%)
Cerebrovascular disease	28 (4%)	5 (4%)	23 (4.4%)
Chronic kidney disease	80 (12%)	32 (25.6%)	48 (9.2)

Abbreviations: N: number, UTI: urinary tract infection, IQR: interquartile range

Clinical symptoms are shown in Table 2. More than half of the patients rated dysuria as the most frequent symptom, in both uncomplicated and complicated UTIs.

Distribution of uropathogens and antibiotic resistance patterns

Table 3 shows the frequency and distribution of uropathogens in related types of UTIs, in which *E. coli* was the main causative uropathogens in each group of UTI.

Table 4 shows that the resistance to antibiotic of *E. coli* urinary isolates that were highly resistant to ampicillin (73.2%), ciprofloxacin (49.0%) and norfloxacin (49.3 %).

The resistance pattern of *E. coli*, classified and analyzed by type of UTI, are shown in Table 5. (uncomplicated UTI and complicated UTI) and Table 6. (asymptomatic bacteriuria).

Asymptomatic bacteriuria

Among *E. coli* in asymptomatic bacteriuria (N= 87), high proportions of isolates were resistant to ampicillin (75.9%), norfloxacin (70.1%). However, the study found low resistance of *E. coli* to amikacin (1.1%), carbapenem groups (0%) and fosfomycin (0%).

TABLE 2. Clinical symptoms of patients with uncomplicated and complicated urinary tract infection.

Symptoms of UTIs	N (%)	
	Uncomplicated UTI	Complicated UTI
Common in lower part UTI		
Dysuria	140 (62.78%)	154 (51.16%)
Urgency	32 (14.32%)	49 (16.28%)
Increase frequency	53 (23.77%)	67 (22.26%)
Hematuria	38 (17.04%)	36 (11.96%)
Cloudy urine	32 (14.35%)	33 (10.96%)
Abdominal pain	111 (49.78%)	22 (7.31%)
Common in upper part UTI		
Fever (documented >38 or subjective)	69 (30.94%)	138 (45.85%)
Flank pain	29 (13%)	25 (8.31%)

Abbreviations: N: number, UTI: urinary tract infection, IQR: interquartile range

TABLE 3. Frequency and distribution of uropathogens in related type of urinary tract infections.

No	Uropathogens	Asymptomatic bacteriuria N= 125		Uncomplicated UTI N= 223		Complicated UTI N= 301		Total N= 649	
		N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
1	*Escherichia coli*								
	Non- ESBLs	66 (52.8%)	44.0 – 61.6	141 (63.2%)	57.0 – 69.5	152 (50.5%)	44.9 – 56.1	359 (55.3%)	51.5 – 59.2
	ESBLs	21 (16.8%)	10.4 – 23.2	22 (9.9%)	6.3 – 13.9	50 (16.6%)	12.6 – 20.9	93 (14.3%)	11.7 – 17.1
2	*Klebsiella pneumoniae*								
	Non- ESBLs	12 (9.6%)	4.8 – 15.2	16 (7.2%)	4.0 – 10.8	22 (7.3%)	4.7 – 10.3	50 (7.7%)	5.7 – 9.9
	ESBLs	2 (1.6%)	0.0 – 4.0	2 (0.9%)	0.0 – 2.2	8 (2.7%)	1.0 – 4.7	12 (1.8%)	0.9 – 2.9
3	*Staphylococcus saprophyticus*	0 (0%)	NA	30 (13.5%)	9.0 – 17.9	2 (0.7%)	0.0 – 1.7	32 (4.9%)	3.4 – 6.6
4	*Enterococcus spp.*	9 (7.2%)	3.2 – 12.0	2 (0.9%)	0.0 – 2.2	16 (5.3%)	3.0 – 8.0	27 (4.2%)	2.6 – 5.7
5	*Proteus mirabilis*	3 (2.4%)	0.0 – 5.6	3 (1.3%)	0.0 – 3.1	12 (4.0%)	2.0 – 6.3	18 (2.8%)	1.5 – 4.2
6	*Streptococcus spp.*	4 (3.2%)	0.8 – 6.4	3 (1.3%)	0.0 – 3.1	10 (3.3%)	1.3 – 5.3	17 (2.6%)	1.5 – 3.9
7	*Staphylococcus aureus*	2 (1.6%)	0.0 – 4.0	1 (0.4%)	0.0 – 1.3	7 (2.3%)	0.7 – 4.3	10 (1.5%)	0.6 – 2.6
8	*Citrobacter spp.*	1 (0.8%)	0.0 – 2.4	2 (0.9%)	0.0 – 2.2	7 (2.3%)	0.7 – 4.3	10 (1.5%)	0.6 – 2.6
9.	*Pseudomonas aeruginosa*	3 (2.4%)	0.0 – 5.6	0 (0%)	NA	3 (1%)	0.0 – 2.3	6 (0.9%)	0.3 – 1.7
10.	Others	2 (1.6%)	0.0 – 4.0	1 (0.4%)	0.0 – 1.3	12 (4%)	2.0 – 6.3	15 (2.3%)	1.2 – 3.5

TABLE 4. The in vitro resistance pattern among *E. coli* urinary isolates from outpatient.

Antibiotic agent	Test (N)	Resistance N (%)	95% CI
Aminoglycoside			
Gentamicin	452	119 (26.3%)	22.3 – 30.5
Amikacin	452	2 (0.4%)	0.0 – 1.1
Carbapenems			
Imipenem	452	1 (0.2%)	0.0 – 0.7
Ertapenem	452	1 (0.2%)	0.0 – 0.7
Meropenem	421	0 (0%)	NA
Cephalosporin			
Cefuroxime	452	128 (28.3%)	24.1 – 32.5
Cefotaxime	452	93 (20.6%)	16.8 – 24.3
Ceftriaxone	452	93 (20.6%)	16.8 – 24.3
Ceftazidime	451	93 (20.6%)	16.9 – 24.4
Cephamycin			
Cefoxitin	448	15 (3.3%)	1.8 – 5.1
Fluoroquinolones			
Ciprofloxacin	447	219 (49.0%)	44.3 – 53.7
Norfloxacin	450	222 (49.3%)	44.7 – 54.0
Folate pathway inhibitors			
Cotrimoxazole	452	186 (41.2%)	36.7 – 45.8
Penicillin			
Ampicillin	452	331 (73.2%)	69.0 – 77.2
Antipseudomonal penicillin+ beta lactamase inhibitor			
Tazocin	449	2 (0.4%)	0.0 – 1.1
Phosphonic acids			
Fosfomycin	403	0 (0%)	NA
Polymyxins			
Colistin	451	0 (0%)	NA

DISCUSSION

Out of the 649 significantly positive bacteriuria samples that were reviewed in this study, a large number of organisms were isolated from female patients in both groups. Older adults represented as a high proportion in this study (median of all age 63 years old, IQR 26 years). These findings were similar to a prior study conducted by Ho, in Singapore.[9] On the other hand, they were inconsistent with some studies conducted in rural areas in India, and a multicenter in Russia; wherein, younger to middle aged adults had the highest prevalence rate in community acquired UTIs.[10,11] This is probably because of the difference of characteristics in our geography; in that tertiary hospitals might have more elderly patients with complex medical problems. In addition to the fact that young, adult females were frequently in the uncomplicated UTI group, which often leads to self-limiting and said group may prefer self-medication, or over the counter drug use. This could explain our low prevalence in young adult community acquired UTIs in our study.

TABLE 5. *E. coli* resistance to antibiotic among Uncomplicated and Complicated UTI.

Antibiotics	Uncomplicated UTI			Complicated UTI		
	Tests (N)	Resistance N (%)	95% CI	Tests (N)	Resistance N (%)	95% CI
Aminoglycoside						
Gentamicin	163	48 (29.4%)	22.7-36.8	202	50 (24.8%)	18.8-30.7
Amikacin	163	0 (0%)	NA	202	1 (0.5%)	0.0-1.5
Carbapenems						
Imipenem	163	0 (0%)	NA	202	1 (0.5%)	0.0-1.5
Ertapenem	163	0 (0%)	NA	202	1 (0.5%)	0.0-1.5
Meropenem	149	0 (0%)	NA	191	0 (0%)	0.0-1.5
Cephalosporin						
Cefuroxime	163	35 (21.5%)	15.3-28.2	202	64 (31.7%)	25.2-38.1
Cefotaxime	163	22 (13.5%)	8.6-19.0	202	49 (24.3%)	18.3-30.2
Ceftriaxone	163	22 (13.5%)	8.6-19.0	202	49 (24.3%)	18.3-30.2
Ceftazidime	162	22 (13.6%)	8.6-19.1	202	49 (24.3%)	18.3-30.2
Cephamycin						
Cefoxitin	162	5 (3.1%)	0.6-6.2	200	8 (4%)	1.5-7.0
Fluoroquinolone						
Ciprofloxacin	162	58 (35.8%)	28.4-43.2	201	103 (51.2%)	44.3-58.2
Norfloxacin	163	59 (36.2%)	28.8-43.6	200	102 (51%)	44.0-58.0
Folate pathway inhibitors						
Cotrimoxazole	163	69 (42.3%)	35.0-49.7	202	87 (43.1%)	36.1-50.0
Penicillin						
Ampicillin	163	123 (75.5%)	68.7-82.2	202	142 (70.3%)	63.9-76.7
Antipseudomonal penicillin+ beta lactamase inhibitor						
Tazocin	163	0 (0%)	NA	201	2 (1%)	0.0-2.5
Phosphonic acids						
Fosfomycin	147	0 (0%)	NA	179	0 (0%)	NA
Polymyxins						
Colistin	163	0 (0%)	NA	201	0 (0%)	NA

Abbreviations: N: number, UTI: urinary tract infection, 95%CI: 95% confidence interval, NA: not applicable

TABLE 6. *E. coli* resistance to antibiotic among asymptomatic bacteriuria.

Antibiotic agent	Test (N)	Resistance N (%)	95% CI
Aminoglycoside			
Gentamicin	87	21 (26.3%)	14.9-33.3
Amikacin	87	1 (1.1%)	0.0-3.4
Carbapenems			
Imipenem	87	0 (0%)	NA
Ertapenem	87	0 (0%)	NA
Meropenem	81	0 (0%)	NA
Cephalosporin			
Cefuroxime	87	29 (33.3%)	24.1-43.7
Cefotaxime	87	22 (25.3%)	16.1-34.5
Ceftriaxone	87	22 (25.3%)	16.1-34.5
Ceftazidime	87	22 (25.3%)	16.1-34.5
Cephamycin			
Cefoxitin	86	2 (2.3%)	0.0-5.8
Fluoroquinolones			
Ciprofloxacin	84	58 (69.0%)	59.5-78.6
Norfloxacin	87	61 (70.1%)	59.8-79.3
Folate pathway inhibitors			
Cotrimoxazole	87	30 (34.5%)	24.1-44.8
Penicillin			
Ampicillin	87	66 (75.9%)	66.7-85.1
Antipseudomonal penicillin + beta lactamase inhibitor			
Tazocin	85	0 (0%)	NA
Phosphonic acids			
Fosfomycin	77	0 (0%)	NA
Polymyxins			
Colistin	87	0 (0%)	NA

Abbreviations: N: number, UTI: urinary tract infection, 95%CI: 95% confidence interval, NA: not applicable

E. coli (69.9 %) was the main causative organism of community acquired UTIs in our study. This is in concordance to previous studies from other locations around the world [4,9-10,12-16], which also showed *E. coli* as the commonest uropathogens isolated in community acquired UTI patients. Furthermore, the extend-spectrum beta-lactamase (ESBL) producing among *E. coli* was reported as 14.3% in this study, which was similar to the research in Lob et al. done in the USA and Canada 2014 (15%)[12], and was lower than the prior study in Young Jun et al. conducted in Korea 2017. (23.3%).[13]

In 2019, the National Antimicrobial Resistant Surveillance in Thailand (NARST) 2019[17] reported that *E. coli* urinary isolates from outpatients were susceptible to ciprofloxacin 30.1%, cotrimoxazole 42.2%, ceftriaxone 59.7%, fosfomycin 98.8% and amikacin 98.8%, which meant that the resistance level to quinolone, cotrimoxazole and cephalosporin were higher when compared with our study. The interpretation of these information must be done with precaution because of difference in inclusion and exclusion criteria.

However, the in vitro resistance rates among *E. coli* urinary isolates in our study had changed when compared with a previous study in 2008[4]. The percentage of resistance was higher in norfloxacin (41.2% in 2008 and 49.3% in 2019) and ceftriaxone (16.4% in 2008 and 20.6% in 2019). On the other hand, the percentage of resistance was greatly declined in cotrimoxazole (56.7% in 2008 and 41.2% in 2019). This is attributable to a decrease in the popularity of prescribed cotrimoxazole and the fact that physicians have been prescribing new antibiotics instead. This result implies that antibiotic resistance can change over time, and the resistance of antibiotics commonly used in primary care is still high.

For uncomplicated UTIs, the prevalence of *E. coli* resistance to cotrimoxazole (42.3%) and ciprofloxacin (35.8%) was higher when compared with the study in Hongkong 2012[14] and Singapore 2015[9] (29-31.8% in cotrimoxazole and 23.4-29% in ciprofloxacin). The Infectious Diseases Society of America (IDSA) guidelines of 2010[18] suggest avoiding empirical specific antibiotics when local resistance among *E. coli* isolated is more than 20% in cotrimoxazole and 10% for quinolone. However, low resistance levels were detected to antibiotics; such as, fosfomycin 0%, carbapenem groups 0% and amikacin 0%, which were not easily obtained as over-the counter drugs, and are relatively expensive in cost compared to others.

For complicated UTI, *E. coli* reported resistance to ciprofloxacin at 51.2 %, and cotrimoxazole at 43.1% in our results. These were higher when compared with a previous study conducted by Arslan in Turkey[15] and Klingenberg in Germany[16] (23.3% - 42% in cotrimoxazole,15.6% - 38% in ciprofloxacin). In addition, the resistance rate of complicated UTIs seems to be higher when compared with uncomplicated groups; especially in quinolone and cephalosporin. So, the selection of empirical antibiotics in complicated UTI should be of more concern, due to probability of treatment failure from antibiotic resistance.

Low resistance levels were detected to antibiotics; such as, fosfomycin, carbapenem groups, and amikacin in both complicated and uncomplicated UTI in this study. The carbapenem groups were high board spectrum drugs that are not commonly used within the community, so fosfomycin and amikacin may be an effective treatment option for community acquired UTIs in our study. The major issue of aminoglycoside use concerns its toxicity such as decrease in renal function, ototoxicty. The rate of amiglycoside-related nephrotoxicity is 8% to 14%[19], which increases at higher doses, with prolonged therapy of 10 days or more, and with the co-administration of nephrotoxic agents.[20]

Strengths of our research include; an update to the distribution and antibiogram of community-acquired uropathogens in 2019. In addition, we classified and analyzed patients according to clinical presentation, and host risk factors (uncomplicated, complicated UTI and asymptomatic bacteriuria), for the aim of minimizing risk of bias between groups.

There were some limitations in our study, which warrant caution in interpreting the results. First, only tertiary-care hospital patients participated in the study. Consequently, our results, theoretically, may not be fully concluded to other populations receiving care in different facilities. Second, we did not perform the minimum inhibitory concentration (MIC) of potent antibiotics, for which we did not receive information of the lowest concentration of an antibiotic that inhibits visible growth.

Nevertheless, our findings demonstrate purely in-vitro antibiotic resistance, for which the efficacy may be quite different from those obtained in vivo. Thus, in addition to considering resistance patterns, the selection of empirical antibiotics should depend on other factors; such as, drug absorption and clearance, cost, and adverse events. Future prospective studies are needed to evaluate the in vivo outcomes and other risk factors of antibiotic resistance, in order to determine the most appropriate treatment for community UTIs.

CONCLUSION

The antimicrobial resistance patterns of uropathogens has changed overtime when compared to the previous study of 2008, with an increased resistance in commonly antimicrobial agent use; especially quinoline and cephalosporin. However, due to low resistance levels, fosfomycin and amikacin could be considered as an effective treatment option for community acquired UTIs in our study.

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