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Original Article

ANTIMICROBIAL SUSCEPTIBILITY OF COMMUNITY-ACQUIRED UROPATHOGENS IN GENERAL PRACTICE

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Conflict of Interest: none

ABSTRACT
Antibiotic resistance of urinary tract pathogens has increased worldwide. The purpose of this study is to provide information regarding local resistance pattern of urinary pathogens to the commonly used antibiotics. One hundred and seventeen cases of community-acquired urinary tract infections were studied. The most common group of patients was the uncomplicated acute cystitis in women. *E. coli* was the most common isolate. Overall, antimicrobial susceptibility test on the organisms isolated showed a resistance of 63.0% to ampicillin, 40.1% to sulfamethoxazole-trimethoprim (S-T), 14.3% to pipemidic acid, 8.6% to norfloxacin, 3.8% to cephalexin, 3.7% to amoxicillin-clavulanate, 1.0% to cefuroxime, and 1.0% to fosfomycin. Three out of five patients on ampicillin as well as two out of five patients on S-T were likely to be inadequately treated.
Keywords: Urinary tract infection, antibiotic therapy, family practice
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INTRODUCTION

Broadly speaking, urinary tract infections (UTI) refer to infections occurring anywhere along the urinary tract from the perinephric fascia to the urethral meatus. Urinary tract infections are common in general practice[1, 2] and have important economic consequences.[2]The disorders are generally treated empirically with antibiotics. It is useful for GPs to be aware of the locally prevalent strains of uropathogens and their sensitivity pattern in order to decide on their choice of antibiotics. This knowledge might help primary care physicians who were often guilty of excessive and inappropriate use of antibiotics.[3]The judicious use of antibiotics requires accurate data on antimicrobial susceptibility which may vary in time and place. Regular surveillance is therefore necessary.

This study investigates the prevalence of uropathogens and their antimicrobial sensitivities in community-acquired UTI. The knowledge of the organisms involved, the epidemiologic characteristics and the antibacterial susceptibility will assist in the formulation of appropriate antibiotic policy for UTI.

METHODS

Patients and settings

The study was conducted in two general practice clinics in Muar, Johor. The study was a cross-sectional survey of all patients 12 years and above presenting with symptomatic UTI from February 2006 to February 2007. Patients with one or more of the symptoms were evaluated for possible UTI: frequency, dysuria, urgency, haematuria, fever, suprapubic pain and flank pain. The exclusion criteria were patients who were hospitalised or received antibiotics during the previous 2 weeks or patients on indwelling catheters. The clinical diagnosis of UTI was confirmed by urine cultures.

Collection of urine specimen and urine cultures

Once a clinical diagnosis of UTI was established, the patient was informed about the study and after consent was taken, a urine sample was obtained. Each patient was carefully instructed regarding the collection of a mid-stream urine sample. The urine specimen collected was inoculated immediately onto a culture plate by the attending doctors (who had received instruction on the correct method of inoculating urine to the culture plate). Inoculation was made on blood agar plate (with 5% defibrinated sheep blood) and MacConkey agar plate using a 0.001ml

commercial inoculation loop. This bedside inoculation method was adopted to avoid sample deterioration (contamination of samples as a result of bacterial overgrowth) due to uncertain laboratory collection times and temperature effects during transport. The inoculated plates were sent to the laboratory on the same day for incubation. Urinalysis (full examination including microscopy) was also requested on each sample. Isolation and identification of the urinary pathogens was done by a private sector accredited laboratory, according to standard bacteriological techniques. Antimicrobial susceptibility testing of the isolates was done using the disc diffusion method according to the Clinical Laboratory Standards Institute guidelines.[4]

Interpretation of culture results

Culture results were interpreted according to the guidelines of the Infectious Disease Society of America.[5] The urinalysis results were used to assist in the diagnosis of UTI for those cultures showing $<10^5$ colony forming units/ml (cfu/ml). We referred to the studies of Stamm and other workers, who had redefined the acute urethral syndrome (women who experience symptoms of cystitis but who have urine cultures with $<10^5$ cfu/ml) as part of a spectrum of lower UTI in women.[6-8]

The diagnosis of UTI was made with the culture of a single bacterial species from the urine sample at a concentration of $\geq 10^5$ cfu/ml. In compliance with the guidelines, females with uncomplicated acute cystitis have infection if the urine cultured between 10^3 and 10^5 cfu/ml, plus pyuria [defined as >10 leucocytes/μL of unspun urine]. A contaminated sample was defined as urine culture with $< 10^3$ cfu/ml or mixed growth.

Uncomplicated acute cystitis in women refers to an infection occurring in young, healthy, non-pregnant adult women without structural or renal dysfunction. Women older than 65 years of age with UTI were considered to have complicated infection as data of possible urologic dysfunctions were often not available to us during the study.

RESULTS

Demographic data

Two hundred and twenty-five urine samples (225 patients) fulfilled the criteria during the study period and were accepted for urinalysis, culture and sensitivity testing. The mean age of the respondents was 43 years (range 12-88 years). Of the respondents 78% were Chinese, followed by Malays 15%, and Indians and others 7%. Females made up 79% of the respondents. Fifty-two percent (117 cases) of the samples were positive for UTI by the criteria defined above. Age distribution of the cases is shown in Table 1.

There was no growth of pathogens in 44.9% (101 cases) of the samples, and 3.1% (7 cases) of the samples were contaminated.

Table 1. Demographic data of patients with urinary tract infections

Age groups (years)	Females, No. (%)	Males, No. (%)
10 – 19	4 (3.4)	1 (0.8)
20 – 29	29 (24.8)	3 (2.6)
30 – 39	16 (13.7)	1 (0.8)
40 – 49	14 (12.0)	3 (2.6)
50 – 59	18 (15.3)	0 (0.0)
> 60	25 (21.4)	3 (2.5)
Total	106 (90.6)	11(9.4)

Uropathogens

E. coli was isolated from 77% (90 cases) of the positive samples. Other uropathogens isolated include *Klebsiella* spp. (10 cases), *Proteus* spp. (4 cases), *Staphylococcus epidermidis* (4 cases), *Staphylococcus saprophyticus* (4 cases), *Streptococcus* spp. (3 cases), *Enterococcus* spp (2 cases), and *Citrobacter* spp. (1 case).

Antimicrobial susceptibility

Overall, antimicrobial resistance was most common to ampicillin with 63.0% and ST with 40.1%. The pathogens were highly susceptible to most of the other antimicrobial tested (>90%) with the exception of pipemidic acid (see Table 2).

Subgroup Analysis

Sixty-four percent (75 cases) of the UTI patients were females with acute uncomplicated cystitis (see interpretation above). This constituted the largest group of patients. Sixty out of the 75 (80%) of the samples grew *E. coli.* Considering the acute uncomplicated cystitis in women alone, resistance of *E. coli* to ampicillin constituted 61%, and S-T resistance was 45%.

Besides male UTI (11 cases), other categories include women with acute uncomplicated pyelonephritis (3 cases) and women with complicated UTI (28 cases). Of these 28 cases, 3 had kidney stones, 6 diabetes, 1 pregnancy, 1 recurrent UTI and 17 were elderly >65 years.

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Table 2: Percentage Distribution of Antimicrobial Resistance of Pathogens in Community-acquired UTI

Antimicrobial	Percentage (No. tested)		
	Overall	*E. coli*	*Klebsiella* spp.
Ampicillin	63.0 (107)	62.0 (90)	90.0 (10)
Amoxycillin-clavulanate	3.7 (107)	3.3 (89)	11.0 (9)
Cefuroxime	1.0 (100)	0.0 (84)	0.0 (10)
Cephalexin	3.8 (104)	1.1 (90)	20.0 (10)
Sulphamethoxazole-Trimethoprim	40.1 (112)	42.0 (90)	30.0 (10)
Norfloxacin	8.6 (105)	8.8 (90)	10.0 (10)
Fosfomycin Trometamol	1.0 (104)	1.1 (90)	0.0 (10)
Pipemidic Acid	14.3 (105)	14.4 (90)	10.0 (10)

DISCUSSION

Laboratory diagnosis of UTI using urine cultures is based on the semi-quantitative counts of organisms and identification of the isolates. A known quantity of urine is streaked on solid agar media and incubated at 35 ± 2° C for 16-18 hours and the bacterial colonies counted. The reliability of this method, however, is strongly dependent on the time taken to send the urine specimen to the laboratory and the transport conditions because urine is an excellent culture medium and delayed plating may result in false-positive results. This was our principal concern in conducting the present study, as the urine specimens had to be transported by couriers on motorbikes. One solution was the use of commercial dipslides, in which the urine is inoculated on the device at the bedside. However, the method was not available locally. We circumvented the problem by direct inoculation of the culture plate as a bedside procedure. From the experience of studies using dipslides, bedside inoculation does not appear to affect the final results of urine cultures.[9] Three percent of the samples in our study were contaminated; this compares favourably with a previous local study[10] where 19% of urine samples were contaminated.

It is important to note that urine cultures are reserved for patients with complicated UTI or those who failed or relapsed after empiric therapy. In the outpatient setting, symptomatic patients with uncomplicated UTI are usually treated empirically, i.e. without urine cultures. However, other investigations may be helpful and each primary care physician has his own strategy. If empiric treatment is based on history alone then one would be treating at least 40% of patients without a UTI. This is because through history taking, the pretest probability of a UTI hardly exceeds 60%.[9] In our study true UTI was present in only 52% of all patients with symptoms. Primary care physicians usually use urine dipstick or urine microscopy to help in the diagnosis and treatment. These investigations have their limitations.[11] Urine dipstick alone seems to be useful to rule out infection if the results of both nitrites and leukocyte-esterase are negative.[12] On the other hand, it is most interesting to note that from a practical standpoint, studies of urine do not seem to have much effect on the actual management of UTI by most primary care physicians. Nearly all patients with symptoms of dysuria, frequency and urgency receive antibiotics irrespective of the results of urinalysis and culture.[13, 14]

The demographic data (Table 1) indicates that women of reproductive age group formed the main group of adult patients with UTI presenting to the general practice clinics (54% of all UTI detected were from women age 10-49 years). These were mainly cases of acute uncomplicated cystitis. Beyond the age of 50 years, cystitis was likely to be complicated by concomitant medical problems like diabetes. It is worthy of note that only a small percentage of older males with UTI (commonly complicated by prostatomegaly and other urinary tract disorders) was represented in this study. It was likely that these patients presented principally to secondary or tertiary healthcare facilities.

The overall frequency of infection and the pathogens involved were broadly as expected. *E. coli* was the most common pathogen isolated, involving 77% of the positive samples. *Klebsiella* spp was the second common organism. *Staphyloccocus saprophyticus*, which is known to occur in a seasonal fashion, was seen only in a few cases. The majority of cases seen in general practice belonged to the class of uncomplicated acute cystitis in women, which comprised 64% of the UTI cases seen in this study. In a classic study by Rubin,[15] *E. coli* was isolated in about 80% of uncomplicated cases of UTI. In our study, a similar 80% of uncomplicated acute cystitis grew *E. coli*. In fact, *E. coli* remained the most common pathogen for all the clinical manifestations and in all groups of patients.[16] The microbiology of UTI, unlike other infectious diseases, has remained remarkably constant over the decades.[17]

E. coli, a member of the human colonic flora, is usually non-pathogenic. However, certain strains may acquire virulence factors and cause human diseases. There are three principal ones, the strains causing sepsis/meningitis, the enteropathogens and the uropathogens. Bacterial cystitis begins with the colonisation of the periurethral skin and the anterior urethra before entry into the bladder.[18] Uropathogenic *E. coli* exhibits specific virulence factors, which allow them to adhere to vaginal and uroepithelial cells, resist bactericidal activity of human serum, prevent phagocytosis by leucocytes and production of specific cytotoxins for tissue invasion.[19] Such virulence factors and uropathogenicity are not confined to *E. coli*, and has been shown with *Proteus mirabilis* and *Klebsiella* spp.[20, 21]

A comparison of the results of the present study with the resistance rates previously published in this country but involving a more generalized bacteriological survey[10], showed a broadly similar picture but with a few exceptions. In comparison to the earlier study by Cheong *et al*, our study showed broadly corresponding figures for resistance rates of *E. coli* to ampicillin (62% versus 50%), to S-T (42% versus 34%), and to cefuroxime (0% for both) but considerably lower figure for amoxicillin-clavulanate (3.3% versus 18%) and higher figure for norfloxacin (8.8% versus 1.6%). The major weakness of our study was the relatively smaller sample size and the temporal limits, which did not allow us to make comments on the change of antimicrobial resistance with time.

Studies from the US and worldwide indicate the emergence of high level S-T resistance in a significant percentage (>20%) of community-acquired *E. coli* UTI isolates. Table 3 shows representative studies from various geographical areas. The data should be viewed in the context of a dynamic and changing pattern of antimicrobial susceptibility with time. High levels of resistance were already found in countries like India, Brazil and Nicaragua. Most parts of Europe, Canada, UK and parts of the USA have fairly low resistant levels. It is interesting to note that Japan has the lowest S-T resistant *E. coli* isolates in the world. The reason was that in Japan S-T was not licensed for use in uncomplicated cystitis and the drug was remarkably expensive. This attested to the fact that antibiotic use correlated with development of resistance. The local usage of S-T has been significant as it has been used for decades in this country. According to the Malaysian National Medicines Use Survey[22] which tracks medication usage both in the public and private sectors, the total usage of S-T for the year 2004 was given as 0.6 Defined Daily Dose/1000 population/day 2004 (compare with cephalexin 1.2, cefuroxime 0.6, norfloxacin 0.1 and amoxicillin-clavulanate 3.0).

It is interesting to note that the complete genome sequences of *E. coli* strains, including one uropathogenic strain, is now available[23]. The chromosomes of *E. coli* are highly diverse mosaic structures, consisting of a core genome of homogenous elements and a large flexible gene pool of mobile genetic elements.[24] The dynamic process of the *E. coli* genomes may then provide for continued emergence of new clones. The recent detection of a globally disseminated *E. coli* clone (clonal group A) accounting for up to 50% of S-T resistant cystitis and pyelonephritis isolates, may explain the increasing resistance pattern and indicates the need for ongoing surveillance.[25-27]

Table 3: Antimicrobial resistance of *E. coli* to sulphamethoxazole-trimethoprim in community-acquired UTI

Author (Year)	Country/location	% Resistant
Karlowsky[28] (2001)	USA (Pennyslvania)	7.4
	USA (Iowa)	33.3
Ishihara[29] (2002)	Japan (Gifu)	3.4
Karlmeter[30] (2003)	Canada	12.0
	Finland	4.9
	Germany	21.0
	Portugal	26.7
	Ireland	20.8
	United Kingdom	12.2
Jose[31] (2003)	Brazil (Sao Paulo)	50.0
Matute[32] (2004)	Nicaragua (Leon)	64.0
Al-Tawfiq[33] (2006)	Saudi Arabia (Dhahran)	33.0
Stratchounski[34] (2006)	Russia	21.0
Akram[35] (2007)	India (Aligarh)	76.0
Present study	Malaysia	42.0

Studies of antimicrobial resistance form the basis for decisions on empiric therapy. Antimicrobial susceptibility of *E. coli* to S-T is pivotal, as it is the standard first-line antibiotic for UTI. Both the local studies (by Cheong *et al* and the present one) clearly showed that *E. coli* is now resistant to ampicillin in >50% of cases and to S-T in >30% of cases. Assuming that these figures are more broadly applicable, then it will be time for us to seriously reconsider the empiric use of these antibiotics in our country, or to seriously investigate at which level the outcome of therapy with these antibiotics is influenced, or to develop strategies to counteract further resistance development to these antibiotics.

The Infectious Disease Society of America has published evidence-based guidelines for the treatment of acute uncomplicated cystitis in women. They recommended the use of a 3 day course of S-T as empiric first-line treatment except in communities with high rates of resistance (>10-20%) to S-T among uropathogens.[36] Subsequently Le and Miller conducted a decision and cost analysis to determine the resistance rate at which S-T should not be used in favour of a quinolone antibiotic. Their results indicated that, when the S-T resistance in a community exceeds 22%, empiric fluoroquinolone therapy becomes less costly than S-T therapy. The added costs of reinfection and complications from progression of infection when using S-T, makes quinolone the antibiotic of choice.[37] However, this analysis did not take into account the concerns about the promotion of resistance to the quinolones. In fact, organisations like the Canadian Family Physicians[38] and the Scottish Intercollegiate Guidelines Network (SIGN Guidelines 2006)[39] recommended against quinolones as first-line agents, with the latter stating that quinolones should not be used for empiric treatment of lower UTI.

Favourable outcomes would also require some degree of physician adherence to these guidelines[40].

In the local context, the high rates of resistance to ampicillin and S-T was likely to be due to their widespread use as first line agents for UTI. These antibiotics were the commonly available agents for the treatment of UTI in the public and the private health sectors. In the National Medicine Use Survey 2004, the usage of ampicillin (including bacampicillin) was about 0.5 Defined Daily Dose/1000 population/year 2004 (compare rates for S-T above). Existing clinical practice guidelines had recommended the use of these agents as first line treatment of UTI for more than a decade.[41] The ß-lactam antibiotics like ampicillin and cephalosporins have other problems besides resistance. They are found to have relatively poor performance in treating symptomatic cystitis. One postulate is that it is rapidly excreted and the duration of significant drug concentration in the urine is short. An additional reason is that ß-lactams are relatively ineffective in clearing gram negative rods from the vaginal and colonic mucosa, thus possibly predisposing to recurrences when used to treat UTI.[36] Commonly available ß-lactam antibiotics for UTI such as cephalexin and cefuroxime may not perform well for these reasons.

In our study of the commonly used antimicrobial agents (Table 3), there was a clear division between the highly resistant group (ampicillin and S-T) and the low resistant group (amoxicillin-clavulanate, cephalexin, norfloxacin, cefuroxime, fosfomycin).

CONCLUSION

In the locality studied, bacteria causing community-acquired UTI showed significantly high resistance rates to ampicillin and S-T. Our study indicated that therapeutic response in the treatment of community-acquired UTI is likely to be inadequate in three out of five patients on ampicillin as well as two out of five patients on S-T. Local antibiotic guidelines should therefore take into consideration this change in resistance pattern. The resistance rates to amoxicillin-clavulanate, cephalexin, cefuroxime, norfloxacin and fosfomycin were low. Treatment regimens should follow prevailing resistance patterns and constant surveillance holds the key to appropriate antibiotic policies to combat resistance.

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A selection of UTI papers from Malaysia

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