Aetiology of community-acquired urinary tract infection and antimicrobial susceptibility patterns of uropathogens isolated

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ABSTRACT

Introduction: Antibiotic resistance among uropathogens causing urinary tract infection (UTI) is increasing worldwide. In most cases of UTI, family physicians can provide empirical treatment without the benefit of a pre-therapy urine culture. Knowledge of the aetiology and antimicrobial susceptibility patterns of uropathogens is important in order to determine the best empiric treatment option. This study aimed to determine the aetiology and antimicrobial susceptibility of uropathogens in culture-positive, community-acquired UTIs over a one-year period.

Methods: This is a retrospective analysis of medical case records. All patients who were diagnosed and coded with UTI and had urine culture done were analysed. The prevalence of the UTI-causing organism and its antibiotic susceptibility was tabulated. Results were analysed with descriptive statistics. The chi-square and Fisher's exact tests were applied for categorical variables.

Results: The commonest organism isolated for all age groups and gender was *Escherichia coli* (74.5 percent) and *Klebsiella* spp. (8.7 percent). Among the oral antibiotics widely used in primary care in Singapore, the Enterobacteriaceae family was most susceptible to amoxicillin/clavulanate. There was no significant difference in the susceptibility of common oral antibiotics when tested against the Enterobacteriaceae for both male and female patients and between patients older than 65 years and those 65 years and below.

Conclusion: Empirical treatment of community-acquired UTI with cotrimoxazole, ciprofloxacin, cephalothin and ampicillin is inadequate. Amoxicillin/clavulanate should be the drug of choice for empirical treatment instead.

Keywords: aetiology, antimicrobial susceptibility, community-acquired urinary tract infection, empirical treatment, uropathogens

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INTRODUCTION

Community-acquired urinary tract infection (UTI) is commonly diagnosed in Singhealth Polyclinic Bedok (SHP-Bedok). However, antibiotic resistance among uropathogens causing UTI is increasing worldwide. Most cases of UTI are uncomplicated, and family physicians may thus provide empirical treatment for these patients without the benefit of a pre-therapy urine culture. Guidelines for the management of UTI and appropriate empirical therapy rely on the predictability of these agents causing the infection and knowledge of their antimicrobial susceptibility patterns. The empirical treatment provided must be guided by clinical evidence as well as the safety profile and cost-effectiveness of the drug, and yet adhere to "antimicrobial stewardship" (using antibiotics in a way that helps to limit the development of resistance).

Antibiotic resistance among uropathogens that cause UTI is increasing worldwide.[1,2] There is no comparative data on antibiotic resistance in the community, particularly those involving uropathogens locally. This evolution of antimicrobial resistance among uropathogens requires continuing re-evaluation of empiric antimicrobial therapy. Only one locally published guideline for the treatment of UTI has been found, the Ministry of Health's Clinical Practice Guidelines (CPG) on the use of antibiotics for adults published in 2006. The CPG states that the recommended first-line therapy for uncomplicated UTI is a three-day course of trimethoprim and sulphamethaxazole. However, the CPG has since been withdrawn. Similarly, while guidelines for treatment of UTI have been developed in the past, their usefulness is

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compromised by conflicting recommendations due to the changing patterns of uropathogen resistance.[3]

Concerns about the increased resistance among uropathogens to sulphonamides have resulted in greater use of fluoroquinolones and other broader spectrum antibiotics. The ready availability of cheap broad-spectrum antibiotics, particularly fluoroquinolones, has also changed the prescribing habits of family physicians in the treatment of uncomplicated UTI. Fluoroquinolones are increasingly being used as a first-line antibiotic for the treatment of UTI.[4] However, the extensive use of such broad-spectrum antibiotics has invariably resulted in the development of greater antibiotic resistance, especially to fluoroquinolones.[5] Widespread empiric use of antibiotics, while convenient, potentially contributes to the development of antimicrobial resistance. In view of the increasing resistance in common community-acquired infections, antimicrobial stewardship must be considered. Thus, knowledge of the aetiology and antimicrobial susceptibility patterns of uropathogens is important in order to determine the best empiric treatment options available for patients. This study aimed to determine the aetiology and antimicrobial susceptibility of uropathogens in culture-positive, community-acquired UTIs over a one-year period.

METHODS

The study is a retrospective analysis of the medical case records of all patients diagnosed with UTI at SHP-Bedok from January 1 to December 31, 2009. The case records of patients who were diagnosed and coded as UTI during the one-year period were retrieved from our computerised Procare Polyclinic Integrated System (PPIS). All patients who were coded with UTI and had urine cultures done were analysed. Only patients with urine cultures yielding growth of pathogens > 10^5 colony forming units/ml from a freshly voided mid-stream urine specimen were included in the study.

Antimicrobial susceptibility of isolates was tested by the disk diffusion method using Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoint. A pure culture of the organism, which had been freshly grown on blood agar or cystine-lactose-electrolyte-deficient media, was suspended in normal sterile saline to form a suspension equivalent to 0.5 MacFarland standard turbidity. The bacterial suspension was then inoculated onto Mueller-Hinton agar (BBL). Antibiotic-impregnated disks were applied to the Mueller-Hinton agar plates. The plates were then incubated at 35°C ambient atmosphere for 16–20 hours. Zone sizes of inhibition were read and interpreted for susceptibility according to the CLSI breakpoint criteria. The antibiotic testing panel was selected according to the type of bacteria grown.

The prevalence of UTI-causing organisms and its antibiotic susceptibility was tabulated, and the organisms were then compared for demographic data. Results were analysed using descriptive statistics. The chi-square and Fisher's exact tests were applied for categorical variables. All statistical tests were two-tailed, and a p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 1,352 patients were coded with a diagnosis of UTI in 1999, and 666 (49.3%) patients had urine cultures performed. Of these, a total of 333 (50%) culture-positive isolates were recovered, thus yielding 24.6% of culture-positive isolates obtained from the 1,352 patients studied. From these, 15 different types of organisms were isolated.

Out of these 333 patients, 34 were male and 299 were female. The majority of the isolates (n = 214) were from patients aged 13–65 years, while 117 isolates were obtained from those aged > 65 years. Only two isolates were obtained from the paediatric age group (< 13 years). This was likely due to the larger number of paediatric UTI cases presented to paediatricians rather than to family physicians owing to the easy access to paediatricians in Singapore. Thus, data collected in the paediatric population was not representative of paediatric patients with UTI in the community. As such, data from the paediatric age group was grouped together with patients ≤ 65 years of age.

The distributions of pathogens according to gender and age group are shown in Table I. *Escherichia* (*E.*) *coli* accounted for the most number of isolates and was also the most prevalent organism among both genders and age groups, while *Klebsiella* was the next most common isolate. *E. coli*, *Klebsiella*, *Proteus mirabilis* or *Staphylococcus saprophyticus* was isolated in 90% of the female patients, while *E. coli*, *Klebsiella*, *Pseudomonas aeruginosa* or *Enterobacter* was isolated in 90% of the male patients. For patients aged ≤ 65 years, *E. coli*, *Klebsiella*, *Proteus mirabilis*, *Staphylococcus saprophyticus* and *Citrobacter koseri* were isolated in 90% of them, whereas *E. coli* and *Klebsiella* accounted for 90% of the isolates among those aged > 65 years.

Organisms belonging to the Enterobacteriaceae family (*E. coli*, *Klebsiella spp.*, *Citrobacter koseri*, *Proteus mirabilis*, *Proteus vulgaris*, *Enterobacter* and *Providencia*) accounted for six of the 15 isolates and up to 89.5% of all isolates. Gram-positive organisms

Table I. Distribution of uropathogens that cause urinary tract infections in patients.

Organisms	No. (%)				
	Total (n = 333)	Male (n = 34)	Female (n = 299)	≤ 65 yrs (n = 216)	> 65 yrs (n = 117)
Escherichia coli	248 (74.5)	19 (55.9)	229 (76.6)	158 (73.8)	90 (76.9)
Klebsiella spp.	29 (8.7)	4 (11.8)	25 (8.4)	10 (4.6)	19 (16.2)
Proteus mirabilis	9 (2.7)	0 (0.0)	9 (3.0)	8 (3.7)	1 (0.9)
Staphylococcus saprophyticus	9 (2.7)	0 (0.0)	9 (3.0)	9 (4.2)	0 (0.0)
Citrobacter koseri	9 (2.7)	0 (0.0)	0 (3.0)	7 (3.2)	2 (1.7)
Enterococcus	8 (2.4)	1 (2.9)	7 (2.3)	7 (3.2)	1 (0.9)
Pseudomonas aeruginosa	5 (1.5)	3 (8.8)	2 (0.7)	4 (1.9)	1 (0.9)
Coagulase-negative *staphylococcus*	4 (1.2)	3 (8.8)	1 (0.3)	2 (0.9)	2 (1.7)
Acinetobacter baumanni	2 (0.6)	0 (0.0)	2 (0.7)	2 (0.9)	0 (0.0)
Candida	2 (0.6)	0 (0.0)	2 (0.7)	2 (0.9)	0 (0.0)
MRSA	2 (0.6)	1 (2.9)	1 (0.3)	1 (0.5)	1 (0.9)
Enterobacter	2 (0.6)	2 (5.9)	0 (0.0)	2 (0.9)	0 (0.0)
Group B *Streptococcus*	2 (0.6)	0 (0.0)	2 (0.7)	2 (0.9)	0 (0.0)
Proteus vulgaris	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.5)	0 (0.0)
Providencia	1 (0.3)	1 (2.9)	0 (0.0)	1 (0.5)	0 (0.0)

MRSA: methicillin-resistant *staphylococcus aureus*

(*Staphylococcus saprophyticus*, *Enteroccocus*, *coagulase-negative Staphylococcus*, Group B *Streptococcus* and methicillin-resistant *Staphylococcus aureus*) accounted for 7.5 % of all isolates. Aerobic Gram-negative organisms (*Pseudomonas aeruginosa* and *Acinetobacter baumanni*) accounted for 2.1%, while *Candida* isolates accounted for 0.6% of all isolates. There were no significant differences in the prevalence of organisms between the male and female group as well as between the two age groups (≤ 65 years and > 65 years) for all organisms. Women aged 13–65 years accounted for the biggest group of patients with a positive urine culture result in our study. This was followed by women > 65 years. Male patients accounted for only 10% of patients who had positive urine culture results.

For the Enterobacteriaceae family, the first-line antibiotic testing panel used were amoxicillin/clavulanate (AmC), ampicillin (Amp), aztreonam (Azt), ceftriaxone (Cef), cephalothin (Ceph), ciprofloxacin (Cip), cotrimoxazole (Cot), ertapenem (Ert), gentamicin (Gen), nalidixic acid (Nal), nitrofurantoin (Nit) and piperacillin/tazobactam (Pip). The antibiotic susceptibility of *E. coli* and *Klebsiella* to the first-line antibiotic testing panel in patients > 65 years of age is shown in Table II (intermediate sensitivity was considered to be resistant).

Of the commonly available antibiotics in primary care and available at SHP-Bedok (AmC, Amp, Cot, Cip, Nit, Ceph), *E. coli* was found to be most sensitive to Nit (95% sensitive), followed by AmC (91%). Amp was the least effective, as only 47.2% of the *E. coli* isolates were sensitive to the antibiotic. Ceph and Cot were effective in about two-thirds of the isolates (65.3% and 62.5%, respectively) and Cip was effective in about three-quarters of the isolates (75.6%). However, among all the antibiotics tested in the antibiotic testing panel, *E. coli* was most sensitive to Ert (100%), followed by Pip (98.7%).

Among the common antibiotics, *Klebsiella* was most sensitive to AmC (82.8%). Nit was effective in slightly more that one-third (37.9%) of the isolates, while Cep and Cot were effective in about two-thirds of the isolates (65.5% and 69.0%, respectively) and Cip, in about three-quarters of the isolates (72.4%). All *Klebsiella* spp. were resistant to Amp (100% resistance). However, among all the antibiotics that were tested in the antibiotic testing panel, *Klebsiella* was most sensitive to Ert (100%) and Gen (100%).

Among the oral antibiotics commonly used in primary care and available at SHP-Bedok, (AmC, Amp, Cot, Cip, Nit, Ceph), AmC (90.4%) had the greatest sensitivity against the Enterobacteriaceae family, followed by Nit (84.2%), Cip (76.9%), Ceph (66.7%), Cot (64.2%) and Amp, which had the least sensitivity (42.4%). Comparisons of differences in antibiotic susceptibility of these six commonly used antibiotics to the Enterobacteriaceae family between male and female patients and between patients aged ≤ 65 years and > 65 years are shown in Table III and IV, respectively. There

Table II. Sensitivity of *E. coli* and *Klebsiella* to the first-line antibiotic testing panel.

Antibiotic	% Sensitivity	
	E. coli	*Klebsiella*
Ampicillin (Amp)*	53.7	0.0
Cephalothin (Ceph)*	61.4	65.5
Cotrimoxazole (Cot)*	62.2	69.0
Nalidixic acid (Nal)*	65.0	69.0
Ciprofloxacin(Cip)*	75.6	72.4
Amoxicillin/clavulanate (AmC)*	90.7	82.8
Gentamicin(Gen)	91.5	100.0
Ceftriaxone (Cef)	91.9	86.2
Aztreonam (Azt)	93.5	82.8
Nitrofurantoin (Nit)	94.7	37.9
Piperacillin/tazobactam (Pip)	98.8	89.7
Ertapenem (Ert)	100.0	100.0

* Commonly available antibiotics in primary care.

Table III. Differences in antibiotic susceptibility of the Enterobacteriaceae family between male and female patients.

Organism	% Susceptibility		p-value
	Male (n = 26)	Female (n = 273)	
Ampicillin (Amp)	42.4	42.3	0.408
Ciprofloxacin (Cip)	76.9	76.9	0.888
Nitrofurantion (Nit)	83.8	88.4	0.832
Amoxicillin/clavulanate (AmC)	90.0	95.6	0.029
Cephalothin (Ceph)	66.9	65.3	0.738
Cotrimoxazole (Cot)	64.4	61.5	0.773

Table IV. Differences in antibiotic susceptibility of the Enterobacteriaceae family between patients aged ≤ 65 years and those aged > 65 years.

Organism	% Susceptibility		p-value
	> 65 yrs (n = 180)	≤ 65 yrs (n = 119)	
Ampicillin (Amp)	42.7	42.0	0.901
Ciprofloxacin (Cip)	78.3	74.7	0.306
Nitrofurantion (Nit)	88.8	77.3	0.026
Amoxicillin/clavulanate (AmC)	87.0	95.6	0.058
Cephalothin (Ceph)	65.9	68.0	0.636
Cotrimoxazole (Cot)	63.8	64.7	0.897

was no significant difference ($p > 0.05$) in susceptibility for the above antibiotics to the Enterobactericeae family between the genders, except for AmC, which has higher rates of sensitivity among the pathogens isolated from female patients with UTI. Also, no significant difference ($p > 0.05$) in susceptibility for the above antibiotics to the Enterobactericeae family was observed between the two age groups, except for Nit, which was more sensitive in those aged > 65 years.

DISCUSSION

This study analysed the aetiologic agent, the distribution of patients and antibiotic susceptibility patterns of microbial species isolated from patients with community-acquired UTI who presented to SHP-Bedok in 1999. These patients were from the community where SHP-Bedok served as a primary care centre.

As this study did not assess whether the patients were symptomatic for UTI, it is possible that some of the patients could have bacteriuria without concurrent UTI; there was no correlation with either pyuria or evaluation of urine formed elements with microscopic examination (FEME), e.g. due to colonisation rather than actual UTI. At SHP-Bedok, the attending doctor may code the diagnosis of UTI based on symptoms and/or urine FEME results and/or urine culture results. Patients presenting with symptoms of UTI usually have both urine FEME and culture done, but this is not the case for all patients. In most cases, the patients are started on empirical antibiotic therapy based on their symptoms and/or urine FEME results. In some cases, urine culture is performed for recurrent UTI, definite symptoms of UTI or if significant pyuria (white blood cells > 6) is detected on urine FEME. It is also more likely for cultures to be ordered for patients with recurrent infections, or for those who have failed therapy or complicated UTI. Hence, results of the urine culture collected in this study may be biased by a preponderance of organisms that had a greater likelihood of resistance, and thus, the prevalence of antimicrobial resistance uropathogens may have been overestimated.

Another limitation of our study could be attributed to wrong classification, as 1,352 patients were coded for a diagnosis of UTI, but only 666 had a urine culture done. While not a standard protocol to order urine culture for all patients suspected of UTI at SHP-Bedok, it is, however, a common practice to do so. In some of these cases, the doctors had coded a diagnosis of UTI for patients returning for follow-up visits for UTI. While efforts have been taken to omit patients on follow-up visits, the coding for UTI could still be a misclassification. Furthermore, the study did not evaluate whether the younger male patients had any predisposing factors for UTI, such as diabetes mellitus, concurrent sexually transmitted disease or urinary tract structural abnormality. It also did not differentiate between low-risk patients and those who were at a higher risk for UTI due to pregnancy, spinal cord injuries, indwelling catheters, diabetes mellitus, underlying urologic abnormalities or a prior history of UTI.

Antibiotic sensitivity of uropathogens changes with time. In the Ministry of Health CPG on the use of antibiotics for adults published in 2006, the recommended drugs of choice for empirical treatment of UTI were trimethoprim and sulphamethaxazole. However, this study has significantly demonstrated a marked resistance of uropathogens to these two drugs since then. Thus, another limitation of this study is its inability to show the development of resistance of the uropathogens over time. While there are no clear recommendations on how frequently antibiogram studies should be repeated in order to determine the relevance of current antimicrobial guidelines, this study must be repeated periodically to assess any significant changes in the antimicrobial sensitivity of uropathogens over time. Therefore, a more rigorous prospective follow-up study that evaluates culture-positive isolates from patients with symptoms of UTI should be undertaken, possibly in three years time.

According to this study, female patients have a higher prevalence of UTI (89.8% female vs. 10.2% male), and this is consistent with the current knowledge that anatomical and physical factors like a shorter urethra predispose women to UTI. While there is no local data on the incidence of UTI in males, community-acquired UTI in the male population has often been reported to be rare, with low incidence rates. Also, UTI in males tends to increase in incidence among diabetics or the elderly due to prostate disorders or neurogenic bladder. However, this study showed that among culture-positive patients, the ratio of male patients aged ≤ 65 years (n = 18) was almost equal to those aged > 65 years (n = 16). As mentioned above, our study did not evaluate whether younger male patients had any predisposing factors to UTI, nor did it take into account whether patients were at a higher risk for UTI.

E. coli is the commonest uropathogen responsible for community-acquired UTI. It accounted for 74.5% of all culture-positive isolates, while *Klebsiella* was the next most common organism, accounting for 8.7% of the isolates in the current study. The data collected is similar to those collected from around the world, where *E. coli* and *Klebsiella* are still the commonest uropathogens isolated among patients with community-acquired UTI. The prevalence of *E. coli* has been reported to be 91.8% among women in Toronto, 72% among women aged 15–50 years and 53% in women aged > 50 years in the United States.[6,7] In both of these studies, *Klebsiella* was found to be the second most common organism isolated, accounting for 3%–12% of the organisms isolated. In a study done in Aligarh, India, *E. coli* was isolated in 61% of the cultures of 920 patients with community-acquired UTI and *Klebsiella*, in 22% of patients.[8] No specific studies on the causation of community-acquired UTI among Chinese or the Southeast Asian population could be found. While there are differences in the study methodologies among these studies, the commonest organisms causing community-acquired UTI found in our study are similar to those found in North America and India.[6-8] The exact proportion of patients with *E. coli* or *Klebsiella* isolates is, however, varied due to the variances in study methodology and the limitations of the respective studies.

In a study conducted for the United States as a whole in 1999, *E. coli* resistance to Cot was 16.8% (range 8.4%–19.2%) and 1.7% for Cip.[9] In a repeat study done in 2001, *E. coli* resistance was found to be 16.1% and 2.5%, respectively.[3] In another Canadian study done in 2001 to evaluate antimicrobial resistance in UTI, *E. coli* resistance to Cot was found to be 8.4%–19.2%, and 0%–1.8% for Cip.[6] The current study yielded 37.8% and 24.4% for *E. coli* resistance to Cot and Cip, respectively, which are both higher than those reported by the above studies.

Uncomplicated UTI is one of the commonest reason for prescribing antimicrobials.[10] Unlike other common conditions seen in general practice such as upper respiratory tract infections, antibiotics are consistently appropriate for the management of UTI. However, the overuse of antimicrobials, particularly broad-spectrum ones, increases the risk of promoting resistance to that particular drug. The Infectious Diseases Society of America (IDSA) guideline suggested that a 10%–20% resistance should warrant a change in the recommendation of the antibiotic to be used as first-line but acknowledged that no specific data supports this recommendation.[11] The 2004 Sanford Guide to Antimicrobial Therapy noted that a 15%–20% *E. coli* resistance to Cot is correlated with microbiologic and clinical failure of the antimicrobial.[12] The current study showed a significant resistance among the Enterobacteriaceae family to commonly available antibiotics in primary care and those used at SHP-Bedok, particularly Amp, Cot, Ceph and Cip. Both *E. coli* and *Klebsiella* have a resistance rate of more than 20% to Amp, Cip, Ceph and Cot. In addition, *Klebsiella* has a resistance rate of more than 20% to Nit. This leaves AmC as the drug of choice for empiric treatment of UTI in a primary care setting if the recommendations of the IDSA and the 2004 Sanford Guide to Antimicrobial Therapy were to be followed.[12]

The susceptibility of the Enterobacteriaceae family to the six commonly available oral antibiotics in primary care (AmC, Amp, Ceph, Cip, Cot and Nit) was almost similar between male and female patients (except for AmC) and between the two age groups (except for Nit). Female patients have a slightly higher sensitivity to AmC. However, the resistance of isolates from both genders to AmC was < 15%, and as such, AmC is still the drug of choice for empirical treatment of UTI at SHP-Bedok. Isolates from patients > 65 years of age were more sensitive to Nit (89%) as compared to those from patients ≤ 65 years of age (77%). Thus, Nit may be effective as an empirical treatment for UTI patients > 65 years of age but ineffective for those ≤ 65 years of age. In general, gender and age should not be the determinants when deciding on empirical antibiotic choice for the treatment of UTI, except when Nit is being considered.

This study showed that *E. coli* is the most prevalent organism causing community-acquired UTI, followed by *Klebsiella*. Both of these isolates have a high resistance rate (> 20%) to Cot, Amp, Cip and Ceph. Only AmC and Nit have a resistance rate of < 15% for *E. coli*, while only AmC has a resistance rate of < 15% for *Klebsiella*. Unless Nit is going to be used for treatment, age and gender in general should not determine the choice of empirical antibiotics for community-acquired UTI. In order to ensure optimal antibiotic use, physicians need to have access to timely information on the local prevalence of antimicrobial resistance, and this information should be updated periodically. Physicians must also continually balance antimicrobial selection for optimal patient outcome with the potential for contributing to further antimicrobial resistance through widespread empiric use.

In conclusion, common uropathogens in community-acquired UTI have a high resistance to widely used antibiotics in the primary care setting. AmC should be the empirical drug of choice for the treatment of community-acquired UTI.

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