Bacterial pathogens and antibiotic resistance patterns in children with urinary tract infection in a Malaysian tertiary hospital

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SUMMARY

Introduction: Urinary tract infection (UTI) is a common bacterial infection affecting children and therefore, prompt recognition and accurate antimicrobial management are vital to prevent kidney damage. This study aims to determine the bacterial pathogens and their patterns of antimicrobial resistance in children presenting with UTI.

Methods: A retrospective study of 721 cases, involving children between the ages of 1-day old to 13 years old with culture-proven UTI in Selayang Hospital, Malaysia between January 2007 and December 2011. The bacterial pathogens and antibiotic resistance patterns in the total population, prophylaxis and no prophylaxis groups were studied.

Results: The 3 most common organisms isolated in the total population were *E.Coli* (41.6%), *Klebsiella spp.* (21.2%) and *Enterococcus spp.* (11.0%). With regards to the antibiotic resistance, *E.Coli* resistance rates to ampicillin, cefuroxime and gentamicin were 67.7%, 15.3% and 7.3% respectively. Ampicillin-resistance was also highest in *Klebsiella spp.* (84.3%), *Enterococcus spp.* (15.5%) and *Proteus spp.* (55.5%).

Conclusion: *E.coli* remains to be the leading bacterial pathogen causing UTI in children, with ampicillin-resistance occurring in more than half of these cases. Therefore, accurate choice of antibiotics is important to ensure optimal outcome. In our study, cefuroxime and gentamicin have lower antibiotic resistance rates and can be used in the treatment of UTI in children.

KEY WORDS:
Urinary tract infection, antibiotic/antimicrobial resistance/susceptibility, uropathogen, children

INTRODUCTION

Urinary tract infection (UTI) is a common bacterial infection presenting to the paediatric services worldwide. A previous study reported that UTI occurs in approximately 8% of girls and 2% of boys by 7 years of age.[1] A large Australian study which was performed in a paediatric emergency department looked at 15 781 cases of febrile illnesses, identified UTI in 3.3% of under 5 years old children.[2]

Studies carried out in infants and children to determine the type of organisms causing UTI have shown that Escherichia coli (E.coli.) was the most commonly cultured organism followed by other organisms including *Klebsiella spp, Pseudomonas, Proteus* and *Enterobacter spp*.[3-5]

UTI is a common cause of morbidity and can further lead to significant mortality if not treated.[6] Furthermore, the symptoms of UTI may be very subtle especially in younger age group. Therefore, prompt suspicion and recognition is the responsibility of all healthcare professionals who come in contact with these children.

Accurate antimicrobial management helps relieve symptoms and prevent kidney damage in most cases.[7,8] However, the increasing rate of antibiotic resistance to the commonly prescribed antimicrobial agents has become a major concern. *E. coli* has been shown to have high resistance against commonly used antibiotics like ampicillin and cotrimoxazole.[1,9] Therefore, it is crucial to determine the aetiological pathogens causing UTI and subsequently the antibiotic susceptibility to aid clinicians in determining the most appropriate choice of empirical antimicrobial treatment.

To the best of our knowledge, aetiological pathogens and the antibiotic resistance patterns in children presenting with UTI has not been previously reported in Malaysia. Hence, we aim to determine the bacterial pathogens and their patterns of antimicrobial resistance in children with urinary tract infection in a Malaysian tertiary hospital.

MATERIALS AND METHODS

This retrospective cohort observational study was conducted in Selayang Hospital, Malaysia and has obtained the ethical approval from the Universiti Teknologi MARA (UiTM) Ethical Committee and the National Medical Research Register of

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Malaysia. Analysis was conducted by reviewing the data from the electronic database of the IT Department and included infants and children between one-day old to 13 years old with positive urine cultures over a 5-year period from January 2007 to December 2011.

Urinary tract infection in infants and children is defined as growth of a single pathogen of $>10^5$ colony forming units/ml by properly collected urine specimen (suprapubic aspiration, transurethral catheterisation, or mid-stream urine) in children with febrile disease or urinary symptoms.[11] Inclusion criteria included history of fever > 38°C or symptoms of UTI for example dysuria, frequency, urgency, hesitancy, small-volume voids, or lower abdominal pain, and symptoms that are non-specific for example vomiting, irritability, jaundice, or failure to thrive in infants.

Our study excluded the hospital-acquired or health care-associated infection. The widely accepted the US Centers for Disease Control and Prevention (CDC) guidelines recommended that infections identified from samples taken more than 48 hours after admission and before discharge should be categorized as hospital-acquired, and those taken before or within 48 hours of admission should be categorized as community-acquired. The 48 hours cut-off was due to the average time required by bacteria in a human to develop from initial infection to detection from a positive diagnostic test.[12] Health care-associated infection is also defined as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent or its toxin and there must be no evidence that the infection was present or incubating at the time of admission to the acute care setting.[13] Patients were excluded if they had intermittent or permanent catheterisation, had history of previous urogenital surgery and had received outpatient antibiotic treatment (other than prophylactic antimicrobial therapy).[14]

Urine culture was performed by taking 1 ml of urine and inoculated using bacteruritest into cysteine lactose electrolyte deficient (CLED) agar (Difco, Becton Dickinson, Maryland) with a calibrated dilution platinum loop. The plate was incubated for 18 to 24 hours at 35°C in an aerobic atmosphere after which the colony count was performed. The result was considered significant when there were >25 colony of single organism which was equivalent to >100,000 organism per ml of urine.[15] Antibiotic susceptibility was determined by using standard techniques.[16] The types of organism and the antibiotic resistance in the total population, prophylaxis and no prophylaxis groups were documented together with information regarding the clinical presentation of the patients.

The data were analysed using SPSS version 22. Univariate analysis was carried out using student's t- test for parametric test and chi- square test for non- parametric test. Data are presented as mean (Standard Deviation) (SD)) and the significance was set at $p<0.05$. The power of the study was set at 80% and OpenEpi Software was used to calculate the sample size with precision of 0.5.

RESULTS

A total of 721 cases were included into the study. Among all the patients, 54% were male and 46% were female. The mean age of the patients included in the study was 3.9 (SD 4.5) years old. The mean age for boys and girls were 2.4 (SD 3.3) and 5.7 (SD 5.1) respectively. Approximately half of our study population (51.1%) was younger than 2 years of age, 16.2% between 2 to 5 years old and 32.7% older than 5 years old. There were two times more males in the less than 2 years old group and the reverse for the more than 5 years old group (Figure 1). The mean age for the 0 to < 2 years group, 2 to 5 years group and >5 years group were 0.5 (SD 0.6), 3.4 (SD 0.9) and 8.9 (SD 2.5) respectively.

We also looked into the distribution among the different races. Most of our patients were Malays with 74.2%, Chinese 13.5%, Indians 11%, other races 1.1% and foreigners 0.3%. All of our samples were collected using clean catch method. Fever was the commonest presenting symptom on admission with 33.6%. Another 36.3% did not present with fever and unfortunately, 30.1% did not have any documentation regarding the presence or absence of fever, but presented with symptoms. Other symptoms included abdominal pain, dysuria, frequency, vomiting and rigors. Hydronephrosis and vesicoureteric reflux (VUR) were the two commonest underlying renal disorders with 10.5% and 10.4% respectively. 8.5% of the patients were on prophylactic antibiotics at presentation with the mean age of 2.5 (SD 2.6) years old.

The 3 most common organisms isolated in the total population were *Escherichia coli* (41.6%), *Klebsiella spp*. (21.2%) and *Enterococcus spp.* (11.0%) (Figure 2A). *E.coli* was still the commonest organisms in both the prophylaxis and no prophylaxis group (60.7% and 39.8% respectively) (Figure 2B).

With regards to the antibiotic resistance, *E.Coli* resistance rates to ampicillin, cefuroxime and gentamicin were 67.7%, 15.3% and 7.3% respectively. Ampicillin-resistance was also highest in *Klebsiella spp.* (84.3%), *Enterococcus spp.* (15.5%) and *Proteus spp.* (55.5%) (Table I).

DISCUSSION

Our study evaluated the types of bacterial pathogens and their patterns of antimicrobial susceptibility in children presenting with UTI. Among all the patients included in the study, 54% were male. This differed from findings observed by Kwan *et al.* who reported more female (56.3%) in their study.[17] Sharifian *et al.* also reported a female preponderance, with a male to female ratio of 1:2.[18] The slight male predominance in our study can be explained by the fact that half of the samples were less than 2 years of age and infection of the urinary tract before the age of one occurs more frequently in boys than girls.[19]

In the present study, *E.coli* was the commonest bacterial uropathogen causing UTI in children and was consistent with other studies.[3-5,17-18,20] However, our study isolated E.coli in only 41.6% of the total population whereas most other studies showed higher percentage between 56.6 to 92%.[3-5,17-18,20] This

Table I: Antibiotic resistance patterns

		Total population (%)	Prophylaxis (%)	No prophylaxis (%)
Ampicillin	*E.coli*	67.7	73.0	66.0
	Klebsiella spp.	84.3	95.0	83.7
	Enterococcus spp.	15.5	50.0	14.3
	Proteus spp.	55.0	50.0	61.8
Cefuroxime	*E.coli*	15.3	10.8	16.0
	Klebsiella spp.	19.0	50.0	17.7
	Enterococcus spp.	2.5	NT	2.6
	Proteus spp.	25.0	NT	26.5
Cotrimoxazole	*E.coli*	48.0	62.2	46.0
	Klebsiella spp.	27.5	66.7	25.9
	Enterococcus spp.	2.5	NT	2.6
	Proteus spp.	52.5	NT	50.0
Gentamicin	*E.coli*	7.3	18.9	5.7
	Klebsiella spp.	17.6	33.0	17.0
	Enterococcus spp.	12.7	50.0	11.7
	Proteus spp.	7.5	50.0	8.8

NT: Not tested

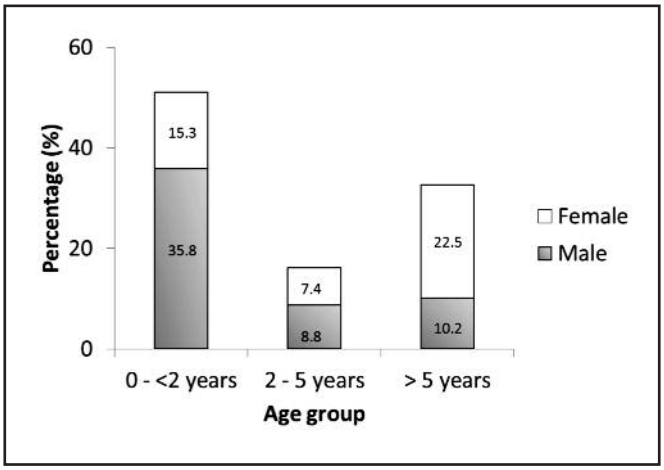

Fig. 1: The percentage of age distributions (0 - <2 years, 2 – 5 years and > 5 years) according to gender. Males(grey-shaded bars) and females(white bars).

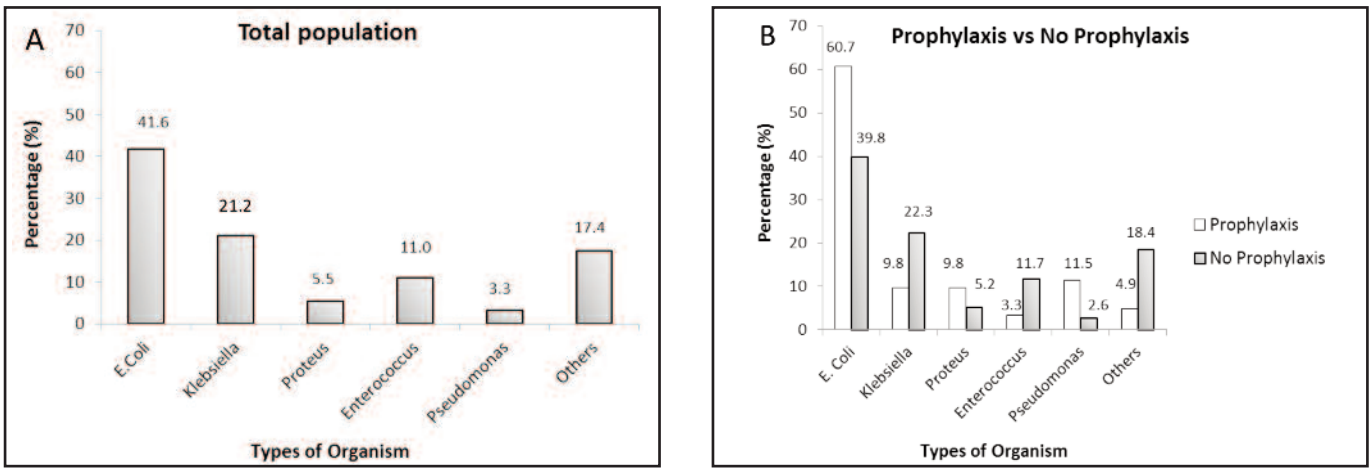

Fig. 2: The percentage of the types of organism for the total population (A) and antibiotic prophylaxis group vs no prophylaxis group (B).

finding could be explained by the fact that our study included the children with complicated UTI due to underlying urogenital tract anomalies. However, when the group receiving prophylactic antibiotics was examined separately, the percentage of E.coli isolated was slightly higher compared to the non-prophylaxis group. This finding may be explained by the fact that the group receiving antibiotic prophylaxis was younger, where more than half of them were less than 2 years of age and some studies have shown that E.coli is the main organism isolated in infants with urinary tract infection.[21, 22]

Klebsiella spp. and *Enterococcus spp.* were the second and third commonest bacteria isolated with 21.2% and 11.0% respectively. Our percentages were considerably higher in comparison to other studies where Klebsiella spp. only ranges between 3 to 13%[5,11,18] and *Enterococcus spp.* ranges between 2-7.9%.[5, 19] Higher non-E.coli UTI in our study again could be due to the inclusion of children with a previous history of UTI and urological anomalies. These children often have antibiotic-resistant *Proteus, Klebsiella,* or *Pseudomonas* strains.[23] We also noted the prophylaxis group to have higher *Proteus spp* and *Pseudomanas spp* isolated from the cultures compared to those without prophylaxis. Cheng *et al* demonstrated the emergence of uropathogens other than *E.Coli* for breakthrough UTI in children receiving prophylactic antibiotics.[14]

Our findings that uropathogens were widely resistant to ampicillin were consistent with other previous studies.[4,9,11,17,20] These data indicated that ampicillin is inadequate to be used as empirical treatment for UTI. Although ampicillin is not a preferred choice of first line antibiotic, *Enterococcus*-positive urine cultures were found to have the lowest resistance rate to ampicillin, similar to several other reports.[24,25]

In one study, E.coli was found to be highly sensitive to ceftriaxone, ceftizoxime and cefotaxime with sensitivity rate of 97.8%, 95.8% and 95.2% respectively.[18] We showed that *E.coli, Klebsiella spp.* and *Enterococcus spp.* were least resistant to cefuroxime compared to ampicillin and cotrimoxazole. This finding supports the use of cefuroxime as the first line antibiotic for community acquired urinary tract infection in children.

Gentamicin was showed to have low resistance rate in the present study and would be a treatment option for parenteral therapy in UTI, consistent with a report by Sakran *et al.* who found that gentamicin was adequate for both first and recurrent UTI.[20] Unfortunately, gentamicin needs to be given parenterally and hence limited to use in a hospital setting. One report suggested that infants and critically ill patients of all ages with community acquired first or recurrent UTI, where pyelonephritis or urosepsis are suspected, should be treated parenterally with third-generation cephalosporines or aminoglycosides in combination with a beta-lactam antibiotic.[25]

Greater antimicrobial resistance in patients receiving antibiotic prophylaxis was consistent with previous studies.[14,26] Conway *et al* also indicated that antibiotic prophylaxis was associated with a higher risk of resistant infections.[27]

A perceived limitation of this study includes the fact that this study was performed retrospectively and limited only to one centre which is a known tertiary referral hospital in the country. This may not reflect the overall antibiotic susceptibility trends across the country and hence emphasises the need for a future multi-centre prospective study. The inclusion of the cases with complicated UTI due to underlying urogenital anomalies may further complicate the findings. fibre recruitment to further increase cardiac output.

CONCLUSION

In summary, E.coli remains to be the leading bacterial pathogen in children presenting with UTI. There is a high antibiotic resistance to commonly used antibiotics among children, especially ampicillin and therefore, accurate choice of antibiotics is important to ensure optimal outcome. In our study, cefuroxime and gentamicin have lower antibiotic resistance rates and can be used in the treatment of UTI in children.

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There is no conflict of interest.

Each author contributed to the study design, data collection, manuscript writing and final approval of the study.

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