International Journal of Pediatrics and Adolescent Medicine 6 (2019) 51–54

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International Journal of Pediatrics and Adolescent Medicine

journal homepage: http://www.elsevier.com/locate/ijpam

Original research article

Community-acquired urinary tract infections in children: Resistance patterns of uropathogens in a tertiary care center in Saudi Arabia

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ARTICLE INFO

Article history:
Received 6 December 2018
Received in revised form
10 February 2019
Accepted 27 February 2019
Available online 8 March 2019

ABSTRACT

Objective: The aim of the present study was to investigate the bacterial pathogens and their resistance patterns in children presenting with their first admission for a urinary tract infection (UTI) in a large tertiary care center in Riyadh, Saudi Arabia.
Methods: A retrospective chart review was conducted of pediatric patients 0–14 years of age who were admitted for their first community-acquired UTI in a large tertiary care center in Riyadh, Saudi Arabia. The review covered a 6-year period (2006–2012).
Results: Data were obtained from 202 children, of which 162 (80.2%) were female. The most frequently isolated uropathogens were *Escherichia coli* (75.7%), followed by *Klebsiella pneumoniae* (9.4%), *Pseudomonas aeruginosa* (5.9%) and *Enterococcus* species (3.5%). Sixteen (7.9%) isolates were ESBLs. Among all uropathogens, 68% were resistant to ampicillin, 54% resistant to co-trimoxazole, and 30% resistant/intermediate sensitivity to amoxicillin/clavulinic acid. Overall, there was a low resistance rate to cefotaxime (4.4%).
Conclusion: *E. coli* is the predominant uropathogen causing UTIs in children, yet there is a high rate of multidrug-resistant organisms. For children admitted for a community-acquired UTI, a third-generation cephalosporin remains an appropriate empiric antibiotic. Our study and the work of others emphasize the importance of choosing empiric antibiotics for pediatric UTIs based on local resistance patterns.

1. Introduction

Urinary tract infections (UTIs) are common in the pediatric population. Up to 8% of girls and 2% of boys experience a UTI by the age of 7 years [1]. UTIs are one of the leading causes of hospital admission for children. Although UTIs are common infections in children, there exists considerable controversy regarding antibiotic choice. As for most infections, antibiotic choice in each community should be guided by the local microbiology and resistance patterns. *Escherichia coli* is the most common uropathogen in paediatric UTIs (60–90% of all infections). Other uropathogens include *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp. and *Pseudomonas aeruginosa* [2]. There have been few studies specifically looking at the bacteriology of uropathogens in pediatric UTIs in the Gulf region. In a recent study in Omani children, the two most common uropathogens were *E. coli (69%)* and *Klebsiella pneumoniae* (17%). Almost half of these two organisms were resistant to co-trimoxazole, and approximately one-third were resistant to amoxicillin/clavulinic acid. In addition, approximately one-quarter of these strains were resistant to cefuroxime [3]. A local study at our institution

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Peer review under responsibility of King Faisal Specialist Hospital & Research center (General Organization), Saudi Arabia.

https://doi.org/10.1016/j.ijpam.2019.02.010

evaluated the role of renal ultrasound in children with a discharge diagnosis of UTI. Out of the 118 patients, *E. coli* was the most common bacteria isolated (80%), followed by *Klebsiella* spp. (8%) and *P. aeruginosa* (2%) [4]. The resistance patterns of these bacteria were not the focus of their study and thus not reported.

There is a growing concern worldwide of increased antimicrobial resistance. Many bacteria including *E. coli* are showing increased rates of antimicrobial resistance. In a recent systematic review and meta-analysis, Bryce et al. found that there is a high global prevalence of resistance to commonly prescribed antibiotics in primary care for paediatric UTIs caused by *E. coli*. In the Organisation for Economic Co-operation and Development (OECD) countries, the pooled prevalence of resistance was greater than 50% for ampicillin and almost 25% for trimethoprim (antibiotics often considered first-line treatment for UTIs). Resistance in non-OECD countries (which includes the Middle East) was significantly higher with approximately 80% for ampicillin [5]. Locally, in a recent study from a large tertiary care center in Riyadh, which included both children and adults, out of 100 *E. coli* urine isolates from hospitalised inpatients with UTIs, 33% were extended-spectrum beta-lactamase (ESBL) producers [6]. In a retrospective study of nearly 13,000 *E. coli* isolates from a general hospital in the Eastern Province of Saudi Arabia, Al-Tawfiq found that the prevalence of antibiotic resistance of *E. coli* was increasing in both outpatient and inpatient isolates. The study found that commonly used antibiotics to treat UTIs are in fact inappropriately used [7]. Another Saudi study at a general hospital analysed ESBLs in urinary gram-negative bacteria. Approximately 10% of *E. coli* were ESBL producers, which causes significant treatment challenges [8]. Moreover, a small study from the emergency department at our institution that included some paediatric patients showed that 23% of *E. coli* isolates exhibited multiple drug resistance [9]. Finally, a recently published study from Nepal found that ESBL was detected in almost 40% of the *E. coli* isolates in paediatric UTIs [10].

While, internationally, uropathogens are becoming increasingly resistant to commonly used antibiotics, there are very limited data of resistance patterns of pediatric uropathogens in Saudi Arabia. The aim of the present study was to investigate the bacterial pathogens and their resistance patterns in children presenting with their first admission for a UTI in a large tertiary care center in Riyadh, Saudi Arabia.

2. Material and methods

2.1. Study design

A retrospective chart review was conducted of paediatric patients 0–14 years of age who were admitted with their first documented UTI in the Department of Pediatrics, King Abdulaziz Medical City-Central Region (KAMC-CR), Ministry of National Guard – Health Affairs. The review included patients between 2006 and 2012. KAMC-CR is a large academic tertiary care center in Riyadh, Saudi Arabia. Urinary tract infection, UTI, pyelonephritis and urosepsis were used as search terms to pull charts for all children admitted for a UTI. Data collected included demographic data, clinical presentation, investigations and detailed information about the bacteria isolated and antibiotic resistance. Inclusion criteria were age 0–14 years with a discharge diagnosis of UTI. As per American Academy of Pediatrics (AAP) Clinical Practice Guidelines [11], we considered a UTI as the presence of both $\geq$50,000 cfu/mL of a single uropathogenic organism and a positive urinalysis (at least one of the following present: WBC $\geq$5 cells/hpf, leucocyte esterase positive or presence of bacteria) on an appropriately collected urine specimen. In patients where the bacterial colony count was 10,000–100,000 cfu/mL (with a urinalysis showing pyuria/bacteriuria), we also considered this as a UTI. Exclusion criteria were age greater than 14 years, hospital-acquired UTI, chronic renal failure, severe birth defects involving the urinary tract (e.g. cloacal exstrophy), immunodeficiency or immunosuppression and solid organ transplant.

2.2. Statistical analysis

Data analysis was performed with SAS statistical software. The prevalence of the different uropathogens and their resistance patterns were reported as percentages. The independent samples *t*-test compared the mean values between two unrelated groups on the same continuous dependent variable. Significant differences were identified at $P < 0.05$.

2.3. Ethical consideration

Approval for our study was obtained from the Research Office at King Abdullah International Medical Research Center (Ref. #: RRSC/251/2012).

3. Results

A total of 202 children fulfilled the inclusion criteria. One hundred sixty-two patients (80.2%) were female, while 40 (19.8%) were male. Amongst the male patients, 27 (67.5%) were circumcised. Forty-five patients (22.3%) were under 1 year of age, of which 39 (86.7%) were female. Fever was present in 170 patients (84.2%) and vomiting in 104 patients (51.5%). The baseline demographic and clinical characteristics are presented in Table 1.

The most frequently isolated uropathogen was *E. coli* (75.7%), followed by *K. pneumoniae* (9.4%), *P. aeruginosa* (5.9%) and *Enterococcus* species (3.5%) (Table 2). Overall, 16 (7.9%) uropathogens were ESBLs. Non-*E. coli* UTIs were much more common in males than in females ($p < 0.0001$) (Table 3). Urinalysis results showed that 92.6% of patients had urine WBC $\geq$5 cells/hpf and 92.1% had bacteriuria.

Table 1
Baseline Demographic and Clinical Characteristics of Children Admitted for their First Urinary Tract Infection.

Variable	n (%)
Less than 1 year	45 (22.3)
1 year–14 years	157 (77.7)
Gender	
Male	40 (19.8)
Female	162 (80.2)
Vomiting	
Yes	104 (51.5)
No	98 (48.5)
Fever	
Yes	170 (84.2)
No	32 (15.8)

Table 2
Prevalence of uropathogens amongst children admitted for their first urinary tract infection.

Uropathogen	n (%)
Escherichia coli	153 (75.7)
Klebsiella pneumoniae	19 (9.4)
Pseudomonas aeruginosa	12 (5.9)
Enterococcus species	7 (3.5)
Enterobacter cloacae	4 (2.0)
Proteus miribalis	4 (2.0)
Citrobacter freundii	3 (1.5)
Total	202

Table 3
Prevalence of *E. coli* versus non-*E. coli* bacteria by Gender.

Gender	*E. coli* (n)	Non-*E. coli* (n)	Total (n), %	*P* value
Male	20	20	40 (19.8)	<.0001
Female	133	29	162 (80.2)	

Nitrites were positive in 93 patients (46%). One hundred ninety patients had a renal ultrasound, and it was abnormal in 54% of patients with hydronephrosis and/or hydroureter as the most common abnormality. A cystourethrogram was performed in 96 patients and 69% had some degree of vesicoureteric reflux.

The antimicrobial resistance pattern of the 202 uropathogens is described in detail in Table 4. Overall, 67.5% of the uropathogens were resistant to ampicillin, 54% resistant to co-trimoxazole and 30% resistant/intermediate sensitivity to amoxicillin/clavulinic acid and cefazolin. There was 12.6% resistance/intermediate sensitivity to nitrofurantoin, 7.6% resistance to gentamicin and 4.4% resistance to cefotaxime. Regarding *E. coli* in particular, 79 strains (51.6%) were resistant to 2 or more antibiotics, while 28 (35.4%) of these strains were resistant to 3 or more antibiotics. A total of 66.2% of *E. coli* strains were resistant to ampicillin, 57.1% resistant to co-trimoxazole, 29.6% resistant/intermediate sensitivity to amoxicillin/clavulinic acid, 22.3% resistant/intermediate sensitivity to cefazolin, 9.6% resistance to gentamicin, 5.7% resistance to cefotaxime and 2.2% resistant/intermediate sensitivity to nitrofurantoin. All paediatric uropathogens tested for carbapenem resistance (meropenem/imipenem) were sensitive.

4. Discussion

To the best of our knowledge, we present the first Saudi study focusing on the prevalence and resistance patterns of uropathogens in community-acquired UTIs in hospitalised children. We found that *E. coli* is the most common cause of UTIs in children causing three-quarters of all infections with a high rate of antibiotic resistance.

The bacteriologic profile and resistance patterns of uropathogens found in our study are consistent with the most recently published regional study in children from Oman [3]. *E. coli,* in particular, accounted for over two-thirds of all UTIs in children, with *K. pneumonia*e being the second most common uropathogen. Our study showed that just over one-half of *E. coli* were multidrug resistant (resistant to 2 or more antibiotics). There was 57% resistance of *E. coli* to co-trimoxazole and 30% resistance to amoxicillin/clavulinic acid. Thus, our study and other studies show that both amoxicillin/clavulinic acid and co-trimoxazole are not appropriate choices for empiric therapy for community-acquired UTIs. Multidrug resistant *E. coli* UTIs are on the rise in children, and recent antibiotic exposure is a major risk factor identified in several recent studies [12–14].

As a result of antimicrobial resistance, common infections such as UTIs are becoming more difficult to treat. There are many risk factors in our setting that may explain the high resistance of uropathogens to commonly prescribed antibiotics. First, there is a recognized overuse of antibiotics in Saudi Arabia. Until recently, antibiotics were freely available over the counter in local pharmacies. In addition, in our community, many broad-spectrum antibiotics including third-generation cephalosporins are used inappropriately (e.g. for treating common paediatric infections like otitis media or pharyngitis). Other factors contributing to high antimicrobial resistance include challenges related to infection control practices and heavy international travel activities due to the large population of expatriates working in Saudi Arabia [15].

For inpatient management of UTIs, the most commonly chosen antibiotic in our institution is a third-generation cephalosporin. Our study showed that of all uropathogens, only 4% were resistant to cefotaxime. Therefore, third-generation cephalosporins remain a good choice for empiric therapy of community-acquired UTIs in our community. As shown in this study, non-*E. coli* uropathogens were more common in males than in females. Further studies are needed to evaluate broadening empiric antibiotic coverage in males.

There are several strengths of our study. This is the first study in Saudi Arabia focusing on the resistance rates of uropathogens causing community-acquired UTIs in hospitalised children. In addition, we were very strict in our inclusion criteria to capture definite UTIs by using the AAP definition (positive urinalysis and urine culture). Furthermore, our study chose a defined population: children with their first documented community-acquired UTI requiring hospitalisation. The main limitations of this study are the relatively small sample size (202) and that our review was conducted from 2006 to 2012. With increasing rates of antimicrobial resistance, it is essential to know resistance patterns of uropathogens over the last five-year period, especially the rate of multidrug-resistant *E. coli* including carbapenem-resistant isolates.

5. Conclusions

E. coli continues to be the predominant uropathogen causing UTIs in children. For children admitted for their first UTI, a third-generation cephalosporin remains an appropriate empiric antibiotic. Our study and the work of others emphasize the importance of choosing empiric antibiotics for paediatric UTIs based on local

Table 4
Antibiotic resistance[a] rates of 202 uropathogens isolated in children hospitalised for a urinary tract infection.

Antibiotic	*E. coli* (n = 153)	*K. pneumoniae* (n = 19)	*P. aeruginosa* (n = 12)	*Enterococcus* species (n = 7)	*Enterobacter cloacae* (n = 4)	*P. mirabilis* (n = 4)	*Citrobacter freundii* (n = 3)	Overall (n = 202)
Ampicillin	66.2	94.7	[b]	14.3	100	75	50	67.5
Amoxicillin/ Clavulinic acid	29.6	33.3	[b]	[b]	100	0	[b]	30
Cefazolin	22.3	100	0	[b]	100	0	100	30
Cefotaxime	5.7	0[c]	[b]	[b]	0	[b]	0	4.4
Ciprofloxacin	14.8	0	0	20	25	25	0	12.8
Co-trimoxazole	57.1	50	0	0	66.7	25	66.7	54
Gentamicin	9.6	0	0	[b]	0	0	0	7.6
Imipenem/ Meropenem	0	0	0	[b]	0	0	0	0
Nitrofurantoin	2.2	66.7	0	16.7	100	66.7	0	12.6

[a]Includes intermediate sensitivity.
[b]Not tested.
[c]0 refers to no antibiotic resistance (i.e., 100% sensitive).

antibiotic resistance patterns.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgment

We would like to thank Dr. Naila Ashraf and Mr. Abin Thomas from the Biostatistics and Modeling Section, King Abdullah International Medical Research Center for their help in statistical analysis.

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