Journal of Advances in Microbiology

21(1): 51-62, 2021; Article no.JAMB.65846
ISSN: 2456-7116

Urinary Tract Infection in Omani Children: Etiology and Antimicrobial Resistance. A Comparison between First Episode and Recurrent Infection

Mohamed El-Naggari[1,2*], Sharef Al-Mulaabed[3], Fatma Rabah[1], Ahmed B. Idrees[1], Zakaria Al Muharrmi[4] and Ibtisam El Nour[1]

[1]Sultan Qaboos University Hospital, Child Health Department, Muscat, Oman.
[2]Al Qassimi Women's and Children's Hospital, Pediatric Department, MOH, Sharjah, UAE.
[3]Presbyterian Healthcare Services: Albuquerque, NM, US.
[4]Sultan Qaboos University Hospital, Microbiology Department, Muscat, Oman.

Authors' contribution

This work was carried out in collaboration among all authors. Author MEN designed and supervised the study. Author MEN wrote the protocol and the first draft of the manuscript. Author managed the analyses of the study. Author handled the microbiological analysis. Authors FR and AI managed the literature searches. Author IEN co-supervised manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMB/2021/v21i130319
Editor(s):
(1) Dr. Niranjalie Perera, Wayamba University of Sri Lanka, Sri Lanka.
Reviewers:
(1) Carlo Genovese, University of Catania, Italy.
(2) Ankita Sen, West Bengal University of Health Sciences (WBUHS), India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65846

Original Research Article

Received 18 December 2020
Accepted 27 February 2021
Published 13 March 2021

ABSTRACT

Aims: The aims of this study were identification of the causative organisms, uropathogens' resistance, and extended-spectrum β-lactamase producing bacteria in primary and recurrent urinary tract infection.
Study Design: A retrospective study included Omani children, less than 14 years, with any documented urinary tract infection.
Place and Duration of Study: Sultan Qaboos University Hospital between September 2008 and August 2012.
Methodology: Comparison was made between both groups using Chi-squared (χ2) test as appropriate.

**Corresponding author: E-mail: mnaggari@yahoo.com;*

Results: The first group included 175 children with first attack of urinary tract infection. *Escherichia coli* was the leading pathogen (69%), *Klebsiella pneumonia* (17%; P<0.001), and extended-spectrum β-lactamase producing bacteria (3%). 230 isolated uropathogens from 74 patients with recurrent urinary tract infection. The most common isolated pathogen was *Escherichia coli* 187 (81.3%; P<0.001), followed by *Klebsiella pneumonia* 12 (5.1%), and extended-spectrum β-lactamase producing bacteria (7%; P=0.042). Overall resistance to parenteral antibiotics was less evident than oral antibiotics, with least resistance to Meropenem and Imipenem (1% each). Higher resistance was found in recurrent urinary tract infection to Augmentin, Cefuroxime, Ceftriaxone, and Cefotaxime. Oral Nitrofurantoin showed least resistance in first and recurrent urinary tract infection, but increased in *non- Escherichia coli* uropathogens.

Conclusion: *Escherichia coli* and ESBL were more common in recurrent urinary tract infection, while *Klebsiella pneumonia* were found more in first urinary tract infection. Meropenem, Imipenem, Amikacin, and Piperacillin/Tazobactam can be used cautiously and selectively, while Cefotaxime and Ceftriaxone cannot be used in both groups. Our report shows high resistance rates to Ampicillin, Cefuroxime, and Amoxicillin/Clavulanate. First-generation cephalosporin is not recommended for use as empiric therapy. We recommend the use of Ciprofloxacin and Nitrofurantoin as empiric treatment in both groups, with close monitoring of clinical response. Indeed, a larger scale multicenter national and regional studies are recommended in Oman and gulf region.

Keywords: Urinary tract infection; uropathogens; sultan qaboos university hospital; Oman.

1. INTRODUCTION

Urinary tract infection (UTI) is a main cause for fever and a standout amongst the most widely recognized community-acquired infections, with prevalence of 5.6 -7.0% in young children presenting acutely ill to primary care [1,2]. Recurrent UTI was defined as having three or more episodes of symptomatic UTI's within a 12-month-period after the first presentation or two or more episodes within six months. The estimated recurrent UTI prevalence is 12-30%. The frequency of recurrent UTI is in tertiary care facilities and can be predisposed by underlying structural abnormalities [2]. In many occasions, it is difficult to differentiate between upper and lower UTI, particularly in children below two years of age. The clinical presentation cannot help in some circumstances, despite the fact that fever and systemic features are progressively predominant in young age group with pyelonephritis [1]. Proper treatment with appropriate anti-microbials is the foundation in management of upper UTI (pyelonephritis). This pivotal advance can avert numerous complications, for example, renal scarring, hypertension, and end-stage renal disease [1,2]. Such huge numbers of various organisms can cause UTIs in young children. The rising trend of antibiotics resistance to the common uropathogens such as Escherichia coli (E. coli), Klebsiella pneumonia (K. pneumonia), and other Enterobacteriaceae species is observed worldwide, which is more prevalent in recurrent UTI [2]. High possibility of antibiotics resistance is associated with uncontrolled use of empirical antibiotics in treatment of UTI on pediatric age group. Therefore, continuous monitoring of pervasiveness of uropathogens in local contexts can help scrutinizing the choice of empirical antibiotics [2,3]. Most of the international and medical society guidelines are recommending a consideration for the local patterns of uropathogens and their antibacterial susceptibility in order to reduce pyelonephritic scarring as a common complication of UTI in children [2,4]. Generally, institutions in different geographical regions reported their uropathological patterns to guide the choice of antibiotics [2,5,6].

However, there is paucity in UTI studies concerning the incidence of different causative uropathogens in Oman. In this study, we aim to report the most common uropathogens, and their antibiotic sensitivity pattern in children presented with first and recurrent UTI, at a tertiary hospital in Oman. In addition, we aim to describe the clinical presentation and laboratory evaluation in those children.

2. METHODOLOGY

This is a retrospective study that archived Omani children presented to Sultan Qaboos University Hospital with UTI between September 2008 and August 2012. Electronic patients' records (EPR) from the hospital information system were retrieved where identification of patients as child

less than 14 years of age having single or recurrent UTI. The classification of recurrent UTI was based on their clinical presentation to our hospital or some other health care facility. Electronic patients' records (EPR) from the hospital information system were retrieved. Exclusion criteria included: patients with neurological disability (laid up patients), immune deficiencies and hematological malignancies, as these patients may have repetitive UTI or use of antibiotic which may influence the anti-microbial resistance pattern. Patients with deficient information accessible in EPR were additionally avoided.

Clinical and laboratory characteristics throughout presentation with the UTI were gathered for every patient. The data collected included age, gender, and clinical presentation, such as fever, chills, decreased activity, nausea and/or vomiting, abdominal pain, poor feeding, constipation, frequency of urination, dysuria, flank pain, secondary enuresis, gross hematuria and foul-smelling urine. Other data collected included the method of urine collection and results of urine analysis, including nitrites, pyuria and hematuria, in addition to the results of urine culture and antibiotic sensitivity tests. Laboratory parameters included the presence of leukocytosis, neutrophilia, and high CRP. Pyuria was defined as ≥5 WBC/high power field (HPF) and classified as mild (5-20), moderate (20-60) and severe (>60) WBC/HPF. Hematuria was defined as 5 RBCs per HPF and was classified as gross or microscopic.

Urine culture technique was either clean catch or catheter samples. The cultures were set up on Cystine Lactose-Electrolyte-Deficient (CLED) Agar media and incubated for 18-24hrs in room air at 35C. Only pure cultures were considered significant, mixed cultures were rejected and fresh new samples were re-requested. Pure cultures of pathogenic organisms were tested for antimicrobial susceptibility based on Clinical and Laboratory Standards Institute (CLSI) guidelines. Significant bacteriuria was characterized as development of ≥100,000 colony forming units (CFU)/mL of a solitary uropathogenic microscopic organisms [6,7]. This is equivalent to the standard definition for Significant bacteriuria on clean catch examples in grown-ups, which depends on concentrates from the 1950s [8]. In catheter urine tests, we characterized significant bacteriuria as development of ≥50,000 CFU/mL of a solitary uropathogenic organisms [3,7].

The current data will be compared with data of the first episode of UTI patients and the pattern of antimicrobial resistance which was obtained from an earlier study by the same research team, on the same age group [9]. The research group want to complete the study which was initiated earlier, to have a complete picture of the primary and recurrent UTI pattern in the studied period.

Data was analyzed utilizing SPSS (Statistical Package for Social Sciences) program 20, IBM, Chicago, Illinois, USA. Analysis included demographic features of the examined patients, with identification of the most common uropathogens causing UTI and their anti-microbial sensitivity. Descriptive statistics were utilized including frequencies and percentages for categorical variables. Comparison was made between children with single UTI and those with recurrent UTIs where a P-value of 0.05 was set as cutoff of statistical significance.

3. RESULTS AND DISCUSSION

During the study period, 405 urine cultures were positive for significant uropathogenic bacteria and amenable for data analysis after exclusion of cases with neurological disabilities, hematological malignancy and cases with immune deficiencies. The cases were classified into two groups: 175 patients with single episode UTI (age range 2 weeks-14 years, median 4 years (IQR 1-7)) whose uropathogens and other clinical characteristics were reported in another study [10]. The remaining 230 uropathogens were isolated from patients with recurrent UTI from total 74 patients (age range 2 weeks-14 years, median 7 years (IQR 4-9). (Fig. 1)

Out of 230 uropathogens in those patients with recurrent UTI, the most common isolated pathogen was *Escherichia coli* 187 (81.3%), among which 16 isolates were ESBL producing organisms. This was followed by *Klebsiella spp* 12 (5.1%), among which one isolate was ESBL. Other organisms identified were: *Enterococcus* 7 = 3%, *Pseudomonas aeroginosa* 5 = 2.2%, *Proteus* 5 = 2.2%, *Enterobacter* 4 = 1.8%, Coliform 3 = 1.3%, *Providencia* 2 = 0.9%, Others 7 = 3% (*Acinetobacter* species, *Aeromonas hydrophila*, *Candida* species, *Citrobacter koseri*, *Escherichia vulneris*, *Klebsiella oxytoca*, *Morganella morganii*, *Staphylococcus saprophytic*). Table 1 shows the details of

antibiotic sensitivity for those 230 uropathogens (classified as E coli and non E coli subgroups). A comparison between incidence of the main identified uropathogens in patients with recurrent UTI and those with single episode UTI is shown in Table 1. Escherichia coli, *Klebsiella pneumonia*, and presence of extended spectrum β-lactamase were all more common in patients with recurrent UTI.

The antibiotics resistance pattern to the uropathogens identified in patients with recurrent UTI is shown in Table 2. Overall resistance to oral antibiotics was more evident than intravenous antibiotics in our study, with least resistance to meropenem and imipenem (1% each), followed by colistin (4%), amikacin (6%), an piperacillin/ tazobactam (8%).

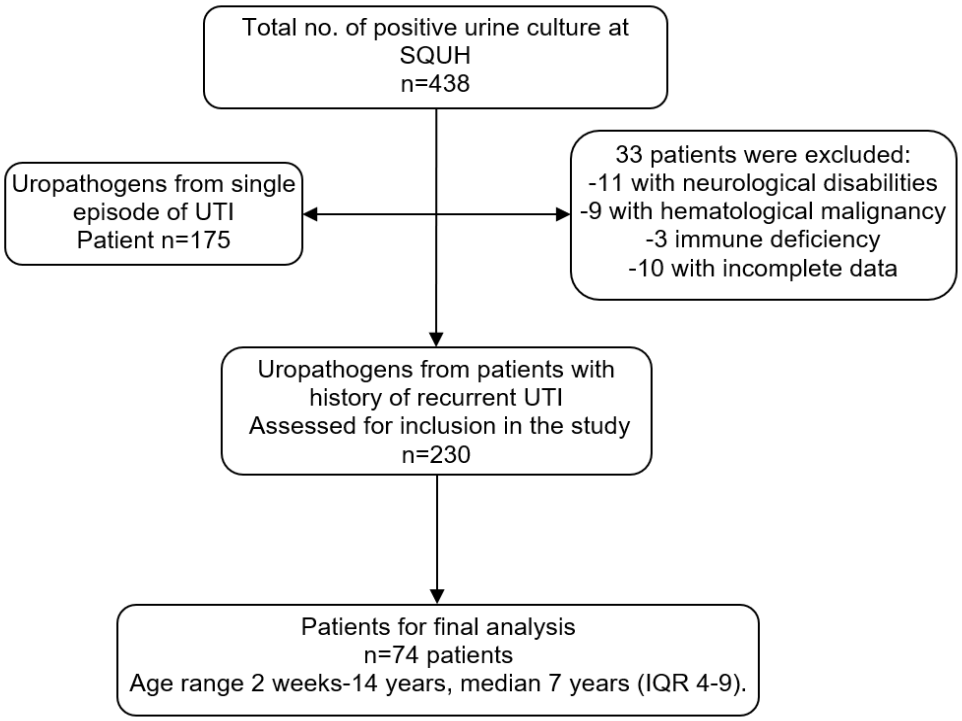

Fig. 1. Flowchart and demographics of children with recurrent urinary tract infection

Abbreviations: UTI = urinary tract infection, SQUH = Sultan Qaboos University Hospital, n = number, IQR= inter-quartile ratio

Table 1. Incidence and comparison between uropathogens in patients with recurrent urinary tract infection (UTI) and those with single UTI (n=405)

	Recurrent UTI n=230 (%)	Single UTI n=175 (%)	P value
Escherichia coli	187 (81%)	120 (69%)	0.001
Klebsiella pneumonia	12 (5%)	30 (17%)	<0.001
Extended spectrum β-lactamase	17 (7%)	5 (3%)	0.042
Enterococcus	7 (3%)	7 (4%)	0.625
Pseudomonas	5 (2%)	2 (1%)	0.476
Proteus	5 (2%)	5 (3%)	0.681
Enterobacter	4 (2%)	3 (2%)	1.000
Coliform	3 (1%)	0 (0%)	0.260
Staphylococcus	1 (0.5%)	4 (2%)	0.172
Citrobacter	1 (0.5%)	3 (2%)	0.322

Escherichia coli was the most prevalent organism in both groups of single and recurrent hence, a comparison was made between antibiotic resistance pattern between *E coli* species identified from the two groups as shown in Table 3. Resistance rate was found to be higher in pathogens of recurrent UTI group. Interestingly, uropathogens in recurrent UTI were more resistant to augmentin, cefotaxime, ceftriaxone and cefuroxime.

Table 4 illustrates the difference in demographic characteristics as well as presenting symptoms between children with recurrent UTI versus those with single UTI. Patients with recurrent UTI were found to be older age, less likely to present with fever, nausea, vomiting, nonspecific abdominal pain, reduced food intake, and decreased activity compared to patients with single UTI. Secondary enuresis was more likely to be found in children with recurrent UTI.

With regards to laboratory findings, there was no significant difference in terms of presence of leukocytosis, neutrophilia, or high CRP between patients with recurrent UTI compared to those with single UTI (Table 5).

Our study describes the uropathogens causing first and recurrent UTIs in Omani children as well as their anti-microbial resistance. The sample was recruited in a tertiary care facility in Muscat, Oman. The results came in line with reports from different remote and regional countries, [2,4,5,11,10] as *E.coli* was the most prevalent uropathogens in our cohort. This finding where concurrent with reports from European countries where the prevalence of *E.coli* was reported to be ranging from 48 to 86% [12,13]. However, North America data showed a prevalence rate of 47 to 58% [14,15].

Klebsiella pneumoniae was the second most common causative organism accounting for 17% and 5% of patients with first and recurrent UTI, respectively [16,17]. Dogan et al. Sakran et al. and Garout et al. found that *Klebsiella pneumoniae* is more in patients with first UTI [2,18,19]. In contrast to our data, higher incidence of *Proteus mirabilis* in pediatric populations were reported in literature, ranging from 15.6 to 22.1% of isolates [3,15]. This finding could be explained by the fact that *P. mirabilis* is available in the preputial sac in young boys, [20] while the vast majority of our cohort were circumcised for cultural and religious believes. Findings from populations sharing similar social backgrounds resembled our findings [2,18,19]. Other recorded uropathogens in our data included: *Pseudomonas*, *Enterobacter*, *Citrobacter*, *Streptococci*, and *Staphylococci*, which were accounted for by different studies [2,11,18].

The vulnerability of uropathogenic microbes to anti-microbial agents is expected to be subject to continuous amendments and change among different geographical regions over time [2]. Cotrimoxazole© is recommended by European Urology Association (EUA) as the first line empirical anti-microbial agent in community-acquired infections only when the resistance rates of uropathogens to TMP are within the range of 10—20% [21]. The anti-microbial resistance to Cotrimoxazole© must be taken in consideration in terms of empiric treatment selection for treatment of UTIs. For instance, reports from different countries have detected resistance rates ranging from 25% to 34% [3,12,22,18,23], an interesting recent report recommends the use of cotrimoxazole empirically because of the recent decline in the resistance rate secondary to slow prescription rate in several European countries [24]. In our cohort, though, higher resistance rates were identified; 50% and 44% in first and recurrent UTI groups, respectively. Interestingly, we were able to detect high resistance rate to ampicillin and ampicillin/clavulanate; 74% and 39%, respectively, being in concurrence with reports from different parts of the world [3,13,16,23]. However, resistance rates as low as 10% have been reported in European countries [13,16,25,26]. Studies conducted in Israel and Turkey evaluated the 1 to 5 years age group in their age stratification. E coli was most resistant to ampicillin and trimethoprim-sulfamethoxazole and least resistant to amikacin and ceftriaxone. In Arab country like Jordan, literature showed same uropathogens rate and resistance pattern [27]. Given the above-mentioned discussion, it can be suggested that Ampicillin, Ampicillin/Clavulanate, and Cotrimoxazole© cannot be efficiently utilized as empirical treatment for UTI [23,28,29,30,31,32]. In our study, the best treatment outcome in patients with *E.coli* infection was achieved using Amikacin, Nitrofurantoin, and Ciprofloxacin, a finding that was consistent with those reported by Ghorashi et al. [5], Sakran et al. [18] and Yuksel et al. [29]. Despite the low resistance rates to Nitrofurantoin like in other studies [9,18,23], low clinical cure has been recognized when compared to customary treatment. This can be

Table 2. Percentage of antibiotic resistance of the isolated uropathogens in patients with recurrent UTI (n=230)

	ALL n=230 (%)	*E coli* spp* n=187 (%)	Non E colin=43 (%)	P value
Ampicillin	170 (74%)	138 (74%)	34 (79%)	0.435
Ampicillin/Clavulanate	90 (39%)	69 (37%)	22 (50%)	0.090
Amikacin	14 (6%)	6 (3%)	6 (13%)	0.002
Ciprofloxacin	30 (13%)	24 (13%)	4 (10%)	0.339
Cefotaxime	76 (33%)	56 (30%)	18 (43%)	0.047
Ceftriaxone	76 (33%)	56 (30%)	17 (42%)	0.055
Cefuroxime	80 (35%)	58 (31%)	22 (51%)	0.004
Nitrofurantoin	18 (8%)	2 (1%)	20 (46%)	<0.001
Gentamicin	28 (12%)	19 (10%)	8 (19%)	0.010
Meropenem	2 (1%)	0	3 (6%)	<0.001
Imipenem	2 (1%)	0	3 (6%)	0.001
Cotrimoxasole	99 (43%)	82 (44%)	17 (41%)	0.487
Tazocin @	18 (8%)	9 (5%)	7 (17%)	0.004
Tetracycline	104 (45%)	82 (44%)	22 (50%)	0.679
Norfloxacin	21 (9%)	19 (10%)	6 (14%)	0.498
Ceftazidime	69 (30%)	52 (28%)	13 (31%)	0.646
Cefipime	62 (27%)	50 (27%)	12 (27%)	0.950
Colistin	16 (7%)	8 (4%)	7 (16%)	<0.001
Levofloxacin	9 (4%)	6 (3%)	3 (6%)	0.251

** 16 out of the isolated E coli (9%) were Extended-Spectrum Beta-Lactamases (ESBL) E coli.*
 # Cotrimoxasole = Trimethoprim/Sulfamethoxazole @ Tazocin = Piperacillin/Tazobactam
Abbreviations: UTI = urinary tract infection, , n = number, E.C= Escherichia coli

Table 3. Comparison between AB resistances of *Escherichia coli* isolated from patients with recurrent UTI versus those with single UTI. (n=307)

	Recurrent UTI – E.C n=187 (%)	Single UTIs – E.Cn=120 (%)	P value
Ampicillin	138 (74%)	(76%)	0.689
Ampicillin/Clavulanate	69 (37%)	(24%)	0.019
Amikacin	6 (3%)	0	0.085
Ciprofloxacin	24 (13%)	(18%)	0.263
Cefotaxime	56 (30%)	(18%)	0.014
Ceftriaxone	56 (30%)	(18%)	0.014
Cefuroxime	58 (31%)	(19%)	0.029
Nitrofurantoin	2 (1%)	(2%)	0.616
Gentamicin	19 (10%)	(11%)	0.473
Meropenem	0	0	NA
Cotrimoxasole #	82 (44%)	(50%)	0.031
Tazocin @	9 (5%)	(2%)	0.138

 # Cotrimoxasole = Trimethoprim/Sulfamethoxazole

@ Tazocin = Piperacillin/Tazobactam. Abbreviations: UTI = urinary tract infection, n = number, E.C= Escherichia coli.

Table 4. Comparison of presenting clinical features between patients with recurrent urinary tract infection (UTI) versus those with single UTI (n=405)

Medical history	Recurrent UTI (n=230)	Single UTI (n=175)	P value
Age, median (IQR)	7 years (IQR 3.9 - 9)	4 years (IQR 1 - 7)	<0.001
Female ratio *	80%	73%	0.264
Fever, n (%)	57 (25%)	88 (50%)	<0.001
Degree of temperature in febrile patients, Mean (± SD)	38.4 (±0.7)	38.7 (±0.8)	0.059
Fever > 40 degrees, n (%)	1 (0.4%)	11 (6%)	0.001
Chills, n (%)	8 (4%)	3 (2%)	0.306
Nausea and/or Vomiting, n (%)	25 (11%)	70 (40%)	<0.001
Nonspecific abdominal pain, n (%)	31 (14%)	51 (29%)	<0.001
Frequency, urgency, dysuria, n (%)	57 (25%)	45 (26%)	0.775
Reduced food intake/Poor feeding, n(%)	13 (6%)	20 (11%)	0.009
Decreased activity, n (%)	6 (3%)	21 (12%)	<0.001
Flank pain, n (%)	11 (5%)	7 (4%)	0.570
Secondary enuresis, n (%)	28 (12%)	8 (5%)	0.013
Gross hematuria, n (%)	5 (2%)	6 (3%)	0.439
Foul-smelling urine, n (%)	19 (8%)	7 (4%)	0.355
Constipation, n (%)	11 (5%)	6 (3%)	0.600

Abbreviations: UTI = urinary tract infection, , n = number, IQR= inter-quartile ratio

Table 5. Comparison of laboratory findings between patients with recurrent UTI and those with single UTI (n=226)

Laboratory Finding	Recurrent UTI	Single UTI	P value
WBC	(n=95)	(n=131)	
-Leukocytosis *, n (%)	31 (33%)	31 (24%)	0.353
-WBC (x10^9/L), range	3-29	2-31	
-WBC (x10^9/L), mean (±SD)	12.6(±5.4)	11.9(±5.7)	
ANC	(n=95)	(n=131)	0.508
-Neutrophilia *, n (%)	32 (34%)	38 (29%)	
-Neutrophil count (x10^9/L), range	1-19	1-24	
-Neutrophil count (x10^9/L), mean (±SD)	7.1 (±4.8)	6.2 (±4.7)	
CRP	(n=61)	(n=73)	
-High CRP **, n (%)	43 (71%)	51 (70%)	0.573
-CRP range	1-344	2-319	
-CRP count (mg/L), median (IQR)	24 (5-85)	24 (3-99)	

** Defined according to the patient age group according to the lab reference.*
*** Defined as CRP > 5 mg/L*
Abbreviations: UTI = urinary tract infection, , n = number, ANC= absolute neutrophilic count, WBC = white blood count, SD = standard deviation, CRP = C reactive protein

attributed to the inadequate tissue concentration in the renal parenchyma, [18] rendering Nitrofurantoin inappropriate for empiric treatment in pediatric patients presenting with pyelonephritis. As found in a number of neighboring countries, [5] resistance to third generation cephalosporins like Ceftriaxone and Cefotaxime was found to be uprising and the pattern is progressively extending to include E.coli organisms. This uprising resistance, however, is not unexpected due to the uncontrolled prescription of third generation cephalosporins, and the finding was inconsistent with reports dating back to previous periods [33]. Furthermore, no resistance was found to members of Carbapenems group, namely, Meropenem and Imipenem, resembling findings reported by *Sahu et al* who identified a 100% sensitivity of Carbapenems to *E.Coli* UTI infection [34].

Some demographic characteristics of our cohort varied significantly when compared to published literature. For instance, mean age of children with UTI infection was found by Sakran et al to be 1.8 years and 3.7 years for first time and recurrent UTI, respectively, which is quite younger than our age distribution. Additionally, they found out that the percentage of female patients was higher accounting for 91.5% and 83.3% when compared to 80% and 73% in recurrent and first time UTI groups, respectively [18]. As far as the clinical picture is concerned, around 75% of our cohort of patients presented with fever as a significant complaint which was comparable to *Muoneke et al* (76%), [35] but strayed away from the findings reported by *Ghorashi et al* (36%) [6]. Recurrent UTI's patients reported by *Nelson et al* exhibited similar pattern to our cohort with regards to fever [36]. Interestingly, laboratories findings in our study demonstrated no distinction between recurrent and first-time patients. White cell count was found to be more in the first episode of UTI compared to subsequent episodes in recurrent UTI patients, [18] but this distinctive feature was not noticeable in our cohort.

4. CONCLUSION

In our study, most common causative organisms were found to be *Klebsiella pneumoniae* for first time UTI. In recurrent UTI group, *Escherichia coli* and ESBL uropathogens were the more prevalent. From our findings, it might be strongly advisable to selectively utilize Meropenem, Imipenem, Amikacin, and Piperacillin/Tazobactam cautiously for recurrent UTI. Nevertheless, we recommend strict controlled prescription by trusted Nephrology or Infectious disease teams to avoid emerging high resistance rates in the future. Interestingly, Cefotaxime and Ceftriaxone were found inefficient to remedy both first time and recurrent UTIs. High resistance rates to Ampicillin, Cefuroxime, and Amoxicillin/Clavulanate were identified in this study. First-generation cephalosporin is unadvisable as an empiric treatment choice for UTIs. In addition, utilization of Ampicillin, Cefuroxime and Augmentin is not supported as a first line of treatment, especially in patients with acute pyelonephritis. In case

those drugs were used as a first line treatment, patients are to be evaluated within 48 hours to decide further treatment based on culture and sensitivity results. The drugs of choice for empiric treatment of both first time and recurrent UTI in our cohort were concluded to be Ciprofloxacin and Nitrofurantoin. We recommend use of Nitrofurantoin in treatment of uncomplicated lower UTIs. Culture and sensitivity studies are considered necessities to guide case management. Indeed, a larger scale multicenter national and regional studies are recommended to synthesize a more extensive description of the predominant uropathogens in Oman and gulf region.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval with MREC number (623) was obtained from the Research and Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University, Oman.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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