ORIGINAL ARTICLE

Risk factors, bacterial profile, and outcomes of urinary tract infection among children treated at a secondary care hospital in Oman

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Abstract

Background: Urinary Tract Infection (UTI) is a prevalent issue in children, which is associated with significant morbidity and mortality. This study aimed to understand the bacterial etiology, antibiotic susceptibility patterns, and associated risk factors for UTIs in children aged 0–13 years. *Aim and Objectives:* Our study aimed to determine the prevalence of pediatric UTI, clinical profile, risk factors, etiology, and antimicrobial resistance pattern with a special emphasis on change in resistance pattern. *Material and Methods:* The retrospective study, approved by Oman's research committee, involved children aged 0–13 diagnosed with UTI from January 2017 to December 2022. The relevant data of the study subjects was retrieved from hospital electronic health records. Data were analyzed using SPSS version 26, with qualitative data reported in frequencies and percentages, while quantitative data were represented by the mean and standard deviation. *Results:* The study involved 295 non-duplicate bacterial isolates recovered from 275 patients. The frequency of isolation was predominant in females (65.5%) and in infants (37.5%). Congenital anomalies such as prenatal hydronephrosis (6.5%) and vesicoureteral reflux (3.6%) were the most common risk factors for UTI in children. Poor fluid intake (5.8%), urolithiasis (1.8%), obesity (1.5%), and infrequent voiding of urine (1.5%) were the other independent risk factors for UTI noticed in our study. Septicemia was observed in 1.5% of the subjects. *Escherichia coli* (55.3%), *Klebsiella pneumoniae* (22.3%), and *Pseudomonas aeruginosa* (5.8%) were the most common etiological agents causing UTI. Extended-Spectrum Beta-Lactamases (ESBL) production was observed in 32.3% and 29.4% of *K. pneumoniae* and *E. coli* strains, respectively. *Conclusion:* In summary, the updated knowledge of local data will help clinicians manage cases, administer appropriate antibiotic treatment, and alleviate antibiotic resistance.

Keywords: Extended-spectrum beta-lactamases, Escherichia coli, Etiology, Risk Factors, Urinary Tract Infection

Introduction

Urinary Tract Infection (UTI) among children represents a common clinical condition occurring in 1–5% of children, more frequently in females [1-2]. The timely diagnosis of UTI in pediatric patients is often challenging because of the frequent presentation of non-specific symptoms or the absence of specific signs and symptoms. The prevalence of UTI in infants and children ranges between 2 and 20% globally [3]. The prevalence varies with age, with the highest incidence reported to be in the first year of life. Preterm infants develop UTIs more commonly than term infants [4]. The incidence of UTI is higher in males in the first year of life, with approximately 3% compared to 2% in girls [5].

Girls develop UTI much more commonly than boys from the second year of life onward [6]. The most prevalent contributing factors in newborns and children include the concentration of bacterial skin flora beneath the nappy, the shorter length of the female urethra, and the surface area of the foreskin in uncircumcised boys. Urinating eliminates microorganisms that temporarily inhabit the lower part of the urethra [7]. Urinary stasis occurs when conditions impair the usual flow of urine, allowing bacteria to have a longer period to cause infection. There are two main types of causes of urine stasis: anatomical factors, like urogenital abnormalities, and functional factors, like neurogenic bladder, behavioral withholding, and constipation. Moreover, in patients with weakened immune systems, the likelihood of UTI rises due to a range of pathogens, including viruses and fungi [8]. The incidence of recurrent UTIs can reach as high as nearly 50%, more often in girls [9-10]. Urinary tract anomalies, including vesicoureteral reflux, bladder bowel dysfunction, and prenatal hydronephrosis, often contribute to the recurrence of UTI in newborns and children. Pediatric UTI frequently goes undiagnosed due to the lack of distinct symptoms, leading to long-term complications including renal scarring, renal hypertension, and end-stage kidney disease. A quick and accurate diagnosis, along with starting treatment on time and fixing any genitourinary problems that were present at birth, can help a lot in preventing UTIs and possible long-term effects [11-12]. UTIs in infants and children frequently result from Gram-negative coliform bacteria originating from the fecal flora. The bacteria establish themselves in the perineum and then ascend upwards to the urinary system. Uropathogenic *Escherichia coli* (UPEC) remains the primary culprit behind UTIs in newborns and children, accounting for approximately 80% of the cases. *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus, Pseudomonas aeruginosa*, *Enterobacter spp*., and *Enterococcus spp.* are the other common uropathogens [4]. In babies with Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT), urinary catheterization, genitourinary surgery, urolithiasis, and recent antibiotic therapy are common predisposing factors for UTI [13].

Children with symptomatic UTI should receive empirical antibiotic therapy early, based on clinical findings and positive urine analysis, while awaiting a urine culture report to achieve a better clinical outcome [14]. Empirical therapy for pediatric UTIs commonly comprises cephalosporins, fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, ampicillin/amoxicillin, and amoxicillin-clavulanic acid [11]. Nevertheless, the increased usage of these antibiotics has led to the emergence and spread of uropathogens that are resistant to several drugs, in addition to frequent treatment failures. The antibiotic susceptibility pattern for uropathogens is subject to variation based on factors such as time, geographic location, and therapy with antibiotics [11]. Therefore, awareness of local data on the clinical characteristics of patients, uropathogens, and antibiotic resistance patterns is crucial for the appropriate selection of antibiotics. There is very limited data on the prevalence of pediatric UTI, risk factors, etiology, and antibiotic susceptibility patterns in Oman, especially in the North-Batinah region. Our study aimed to determine the frequency of pediatric UTI, clinical profile, risk factors, bacterial etiology, and antimicrobial resistance pattern among study subjects treated from 2017 to 2021 in a secondary-care hospital situated in the North-Batinah governorate of Oman.

Material and Methods

A retrospective study was conducted at Sohar Hospital in collaboration with the College of Medicine and Health Sciences (COMHS). The study received ethical approval from the Research and Ethical Review and Approval Committee (RERAC) of the Ministry of Health, Oman [Approval No.: MH/DGHS/NBG/RERAC23/2022]. The study subjects included all infants and children (0–13 years) clinically diagnosed with UTI, confirmed by positive urine culture, during the period from January 2017 to December 2021.

The relevant data retrieved on the study subjects from the health records of Sohar Hospital included demographic characteristics of the study subjects, bacterial profiles, antibiotic susceptibility patterns, and clinical details such as risk factors and complications of infection.

Inclusion criteria: Infants and children (0–13 years) who were clinically diagnosed with UTI and confirmed by positive urine culture in the study.

Exclusion criteria: Infants who were clinically suspected but had a negative culture, as well as cases with incomplete data, from the study.

Sample collection and identification of uropathogens: Urine samples were collected as per the standard guidelines of the Clinical Laboratory Standards Institute (CLSI). Urine samples were initially subjected to urine dipstick analysis and urine wet-mount microscopy. A specified volume (1µL) of a urine sample collected using a calibrated bacteriological loop was inoculated onto CLED agar and MacConkey agar medium and incubated aerobically for 18–24 hours at 37°C. The bacterial growth of ≥105 CFU/mL in the midstream urine sample was considered significant as per the standard guidelines of CLSI [15]. Additionally, the growth of any number of bacterial colonies in a suprapubic, aspirated urine sample is considered significant. Urine culture with the isolation of three or more bacterial species was considered contamination. Pure bacterial isolates on the culture plate were initially screened by colony morphology and Gram stain. We identified gram-positive bacteria at the species level by analyzing the outcomes of catalase, bile esculin agar, pyrrolidinyl aminopeptidase, and coagulase tests. The identification of gram-negative bacteria at the species level was accomplished using typical biochemical tests, including urease, indole, citrate utilization, triple sugar iron, Hydrogen Sulfide (H_2S) generation, lysine iron agar, motility, and oxidase tests, following the guidelines set by the CLSI [15].

Antibiotic susceptibility testing:

The Kirby-Bauer disc diffusion method was used to perform Antimicrobial Susceptibility Testing (AST) on Mueller Hinton (MH) agar, according to the guidelines set by the CLSI. The diameter zone inhibitions were interpreted as Sensitive (S), Intermediate (I), or Resistant (R) [15].

The following antibiotics were employed for gram-negative isolates: ampicillin, amoxicillin/ clavulanic acid, ciprofloxacin, gentamicin, amikacin, imipenem, meropenem, piperacillin-tazobactam, cefotaxime, cefuroxime, ceftriaxone, ceftazidime, nalidixic acid, and trimethoprim-sulfamethoxazole. The following antibiotics were utilized for gram-positive isolates: ampicillin, amoxicillin/ clavulanic acid, ciprofloxacin, cefotaxime, cefuroxime, ceftriaxone, nalidixic acid, vancomycin, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, linezolid, and vancomycin discs.

Statistical analysis

The extracted data from hospital health records was entered into an Excel spreadsheet, cleaned for errors, and coded for statistical analysis. Statistical Package for the Social Sciences (SPSS) software (IBM Chicago) version 26 was utilized for data analysis. The quantitative variables were expressed as mean ± Standard Deviation (SD), while the qualitative variables were presented as frequencies and percentages.

Results

A total of 295 non-duplicate bacterial strains isolated from 275 study subjects were included in the study. Table 1 represents the baseline characteristics of the study subjects. Infection was more common among younger children (3.60 ± 3.87). Females (65.5%) had a higher frequency of isolate recovery compared to males (34.5%). UTI was most common (42.5%) among infants of age < 1 year, followed by children of age 6–10 (26.2%), 2–5 years (22.9%), and 11–13 years (8.0%). In the first year of life, the infection was predominant in males (59.3%) as opposed to females (40.7%). Females had a higher frequency of infection compared to males from the second year onward.

Table 1: Age-sex wise distribution of study subjects

Characteristics	Number (Percentage)
Gender	
Male	95 (34.5)
Female	180 (65.5)
Age distribution	3.60 ± 3.87
< 1year	118 (42.9)
- **Male**	70 (59.3)
- **Female**	48 (40.7)
1-5 years	63 (22.9)
- **Male**	13 (20.3)
- **Female**	50 (79.7)
6-10 years	72 (26.2)
- **Male**	09 (12.5)
- **Female**	63 (87.5)
11-13 years	22 (8.0)
- **Male**	03 (13.6)
- **Female**	19 (86.4)

Figure 1 represents the risk factors and complications of UTI. The most common risk factor for UTI, primarily in infants (< 1 year of age), was CAKUT. Some children had prenatal hydronephrosis (18, 6.5%), vesicoureteral reflux (10, 3.6%), and other congenital anomalies (11, 4.0%). Other risk factors noted in our study subjects were urolithiasis (5, 1.8%), inadequate breastfeeding (10, 3.6%), inadequate fluid intake (16, 5.8%), prematurity (5, 1.8%), obesity (4, 1.5%), neurogenic bladder (2, 0.7%), and infrequent voiding of urine (4, 1.5%). We observed recurrent UTI in 11 (4.0%) patients. In our study subjects, 8 cases (2.9%) of septicemia observed was the most common complication.

Table 2 depicts bacterial agents isolated from urine samples. The majority of isolates recovered were Gram-negative bacilli (92.5%) compared to Gram-positive cocci (7.5%). *E. coli* (55.3%) and *K. pneumoniae* (22.3%) were the most common etiological agents isolated from urine samples. Less commonly isolated pathogens were *Pseudomonas aeruginosa (5.8%), P. mirabilis (3.6%), Enterobacter spp. (3.6%),* and other gram-negative bacteria (2.7%), including *Serratia spp., S. maltophilia, A. baumannii, and M. morgagnii.* UTI by Gram-positive bacteria (7.5%) was less frequent. *Enterococcus spp*. (3.4%) was the most common agent, followed by *Staphylococcus spp*. (2.7%), and Group D *streptococci* (1.4%).

Table 3 reveals the antibiotic susceptibility pattern of etiological agents. Gram-negative bacteria showed good susceptibility towards amikacin (89-100%), imipenem (89-100%), meropenem (89-100%), piperacillin-tazobactam (97% to 100%), gentamicin (88% to 100%), and ciprofloxacin (83% to 100%). While they showed high-level resistance to ampicillin (70–100%) and amoxicillin-clavulanic acid (40–100%), except for *P. mirabilis,* and ceftriaxone (96–100%) and ceftazidime (50–100%), except for *P. aeruginosa,* Overall, gram-positive isolates showed good susceptibility to trimethoprim-sulfamethoxazole (87.5–100%) and gentamicin (75–100%). Enterococcus spp. showed high levels of resistance to cefuroxime (100%), ciprofloxacin (90%), cefotaxime (50%), and ampicillin (44.4%). All gram-positive isolates were sensitive to vancomycin and linezolid (100%).

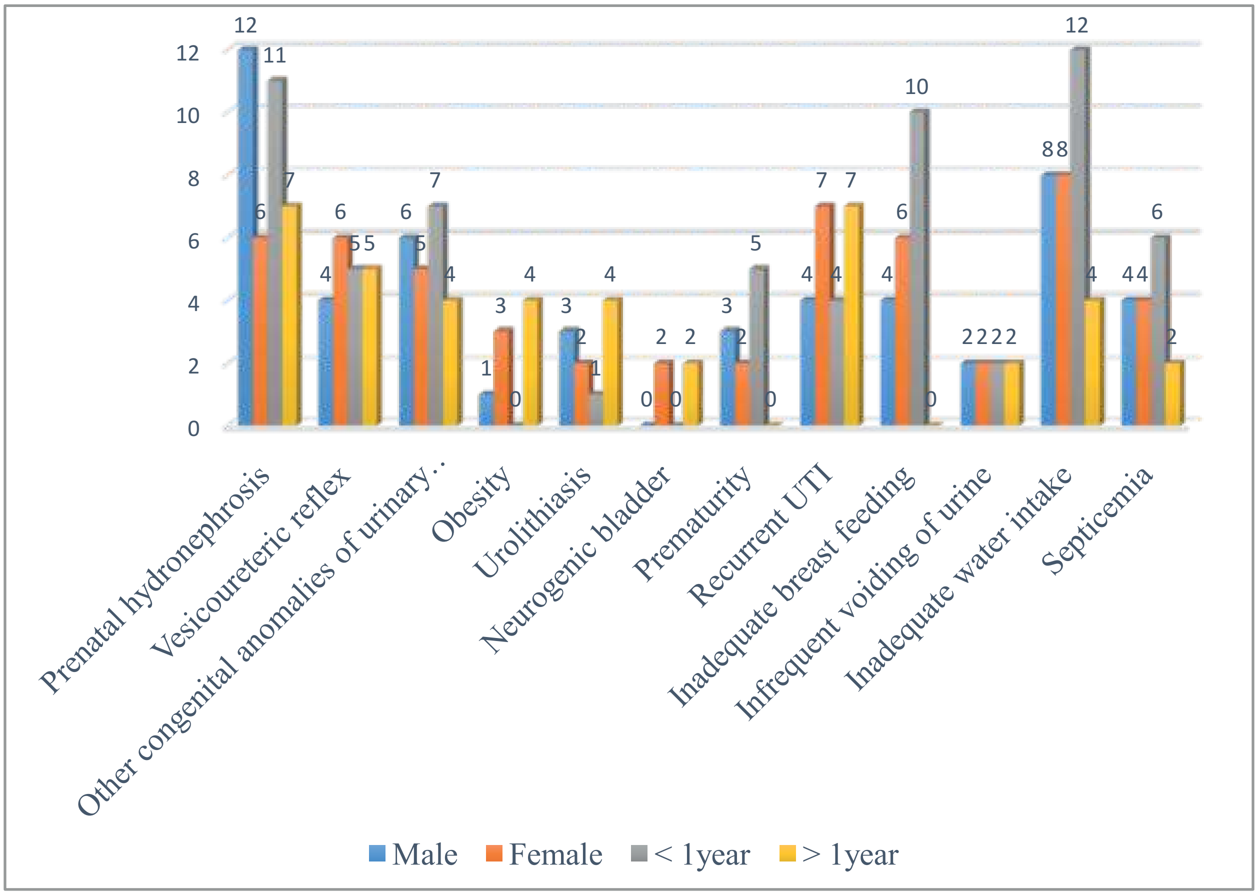

Figure 1: Risk factors and complications of UTI among the study subjects

Table 2: Etiological agents of UTI (n = 295)

Gram-negative bacteria, n=273 (92.5%)	**Number (Percentage)**
Escherichia coli	163 (55.3)
Klebsiella pneumoniae	65 (22.3)
Pseudomonas aeruginosa	17 (5.8)
Enterobacter spp.	10 (3.4)
Proteus mirabilis	10 (3.4)
Others*	8 (2.7)
Gram-positive bacteria, n=22 (7.5%)	10 (3.4)
Enterococcus spp.	8 (2.7)
Staphylococcus spp.	4 (1.4)
Streptococcus spp.	

Table 3: Antibiotic susceptibility pattern of isolated uropathogens

Antibiotic susceptibility (%)	**Gram-negative bacterial isolates (%) (n=273)**						**Gram-positive bacterial isolates (%) (n=21)**		
	***E. coli* (n=163)**	***K. pneumoniae* (n =65)**	***P. mirabilis* (n=10)**	***Enterobacter spp.* (n=10)**	***P. aeruginosa* (n=17)**	***Other gram-negative bacteria** (n=9)***	***Enterococcus spp.* (n=10)**	***Staphylococcus spp.* (n=8)**	***Streptococcus spp.* (n=3)**
ESBL (n=69)	29.4 (n=48)	32.3 (n=21)	-------	-------	-------	-------	-------	-------	-------
AMIK	100	100	-------	100	100	88.9	-------	-------	-------
AMPI	29.4	0	80	0	-------	0	55.6	66.7	100
AUGM	60.9	58.1	90	0	-------	0	66.6	100	100
CFTX	82.5	61.5	100	100	-------	100	50	----------	100
CFXM	66.3	64.0	100	--------	-------	16.7	0	---------	100
CIPR	83.2	93.7	100	100	100	100	10	87.5	100
CORT	69.8	73.4	90	100	-------	100	100	87.5	100
CRONM	3.8	0	-------	100	-------		100	--------	100
CTAZ	3.8	0	-------	--------	94.1	50	--	--------	-------
GENT	88.3	82.8	100	100	88.2	88.9	100	75	-------
IMIP	100	100	-------	-------	93.3	88.9	-------	---	-------
MERO	100	100	-------	-------	93.8	88.9	-------	----	-------
LINZ	------	------	-------	-------	-------	-------	100	100	-------
NALI	57.1	87.5	100	88.9	-------	-------	100	----	-------
TAZP	96.9	96.9	100	100	-------	100	100	----	-------
VANC	-------	-------	-------	-------	-------	-------	-------	100	-------

AMIK: Amikacin, AMPI: Ampicillin, AUGM: Amoxicillin-clavulanic acid, CFTX: Cefotaxime, CFXM: Cefuroxime, CIPR: Ciprofloxacin, CORT: Trimethoprim-sulfamethoxazole, CRONM: Ceftriaxone, CTAZ: Ceftazidime, GENT: Gentamicin, IMIP: Imipenem, MERO: Meropenem, LINZ: Linezolid, NALI: Nalidixic acid, TAZP: Piperacillin-tazobactam, VANC: Vancomycin

Discussion

This study aimed to ascertain the prevalence of UTI, identify the bacterial pathogens, and analyze their antibiotic susceptibility pattern in children who visited the pediatric clinic at Sohar Hospital between January 2017 and December 2021. Additionally, we ventured to determine the risk factors and complications of UTI in the study group.

UTI is a frequently occurring issue in newborns and young children. Age and gender significantly influence the prevalence of UTIs. Starting in the second year, UTI primarily affects girls [8, 16]. However, during the initial year of life, UTI is more prevalent in boys, primarily due to the absence of penile circumcision. Uncircumcised children experience bacterial buildup behind the foreskin (prepuce), making it challenging to maintain optimal cleanliness of the penile tip in neonates [16-17]. A comprehensive meta-analysis has demonstrated that the lifetime risk of UTI in males who are not circumcised is five times greater than in males who are circumcised [17]. In line with this, our study revealed a higher frequency of UTI among male infants, probably because of a lack of circumcision in the first year of life. Overall, 65.5% of females and 34.5% of males had UTIs in our study ($p < 0.001$). A previous study from Oman also reported that a significantly greater number of male infants (67%) aged <1 year had UTIs than females (33%) ($p < 0.001$) [18].

Any factor that disrupts the normal urinary flow can potentially increase the risk of UTI. When there is a problem with the flow of urine, it can build up in the bladder and kidneys and stay there. This makes it easy for bacteria to grow, which can cause inflammation and damage to the lining of the bladder and kidneys. A broad range of disorders result from developmental Abnormalities of the Urinary Tract (CAKUT). Previous studies reported Vesicoureteral Reflux (VUR) as the most common CAKUT associated with UTI, approximately in 20–30% of children [13, 19]. VUR disrupts the normal urine flow, leading to the backward flow of urine towards the ureter and kidney. This increases the chance of infection spreading to the kidney, potentially causing pyelonephritic scarring and chronic renal failure in children [13]. Prenatal hydronephrosis, accompanied by ureteral dilatation, significantly increases the likelihood of UTI in infants during their first year of life [20]. A recent research article on UTIs in infants from Gulf Cooperation Council countries found that congenital abnormalities, such as hydronephrosis, are important factors that contribute to the frequent occurrence of UTIs ($p < 0.05$) [21]. In line with this, 6.5% and 3.6% of children in our study had hydronephrosis and VUR, respectively. Other well-known risk factors that impair or cause obstruction to urine flow in children are urolithiasis and neurogenic bladder [22]. Our study showed the presence of these risk factors in a minority of the study subjects. While obesity is considered a risk factor for UTI, prior studies have shown inconsistent findings about the association between obesity and UTI [23]. One potential reason for the link between obesity and a higher occurrence of UTI is that adipose tissue triggers inflammation, which then weakens the immune system. This weakened immune response may then make it easier for infectious agents to survive in the body. Hsu and Chen (2018) observed a greater prevalence of UTI in obese children (33.5%) compared to healthy children (17.3%) [23]. Consistent with the above findings, we noticed obesity as an independent risk factor in a minority (1.5%) of our study subjects. Literature suggests exclusive breastfeeding reduces the risk of infection in children. Breastfed babies receive protective antibodies from breast milk, which helps to develop a strong immune system and thus protects the infants from infections [24]. Ten infants in our study had a history of inadequate breastfeeding, but it is difficult to comment on this finding due to the limited extent of our data collection. Two prior case-control studies conducted in young girls, one preschool-aged and the other school-aged, have demonstrated a correlation between inadequate fluid intake, infrequent urination, and the recurrence of UTI [25-26]. A minority of children with UTIs in our study had a history of poor fluid intake and infrequent voiding of urine, and recurrent UTIs were common among them.

Generally, in more than 95% of the instances, the route of transmission of UTI is by ascending pathogens from the periurethral area. Coliform bacteria, which contaminate the area around the anus, ascend upwards from the lower part of the urethra to the bladder and then to the kidney. Women are more susceptible to getting UTIs due to their shorter urethras in comparison to men. This anatomical difference facilitates the easier passage of bacteria into the urine bladder [18]. Females accounted for nearly 2/3 of the infections in our study, consistent with previous studies [4, 6-7].

E. coli is the predominant coliform bacteria, and it accounts for 70–80% of UTIs in children, predominantly in females [11]. Some strains of UPEC have different attachment factors, like type I pili, P fimbriae, and X-adhesins. These help the bacteria stick to the uroepithelial surface of the bladder and ureter, which lets them get past defenses and makes it easier for the bacteria to get inside the body, which leads to UTI [27].

Previous studies have demonstrated *E. coli* as the predominant uropathogen causing UTI, significantly more frequently in females than males [11, 12, 18, 28]. Similarly, in our study, *E. coli* was the most frequently isolated bacteria from urine samples, occurring at a much higher frequency in girls than boys. In our study, we also observed the recovery of other common pathogens from urine samples, including *K. pneumoniae, P. aeruginosa, Proteus spp., Enterobacter spp.,* and *Enterococcus spp.,* which is consistent with the literature [22].

The physicians' knowledge about microorganisms that cause UTI and effective antibiotics in a particular geographical area is vital to selecting the appropriate antibiotics. Imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and amikacin were found to be better against gram-negative isolates in our study. They were less sensitive to ampicillin, ceftazidime, ceftriaxone, and amoxicillin-clavulanic acid. Overall, gram-positive bacteria showed good susceptibility to trimethoprim-sulfamethoxazole, linezolid, and gentamicin. Enterococcus showed lower susceptibility to most of the beta-lactam antibiotics but higher susceptibility to piperacillin-tazobactam, trimethoprim-sulfamethoxazole, gentamicin, nalidixic acid, and linezolid.

Furthermore, a small proportion of *K. pneumoniae* strains (32.3%) and *E. coli* strains (29.4%) exhibited the production of Extended-Spectrum Beta-Lactamase (ESBL). Hence, the effectiveness of the third generation of cephalosporins against these germs was diminished as a result of the increased rate of ESBL production. Similar to our study results, Pouladfar *et al*., (2017) have also demonstrated higher resistance of gram-negative bacteria to ampicillin (81%), third-generation general cephalosporins, and higher susceptibility to imipenem (90%) and gentamicin (65%). Furthermore, ESBL production was observed in 69.2% and 30.8% of *E. coli* and *K. pneumoniae*, respectively [29]. Knowledge about the local prevalence of uropathogens and their antibiotic susceptibility patterns benefits physicians in choosing appropriate empirical antibiotics, thus improving patients' treatment responses, and reducing the rate of antimicrobial resistance.

Septicemia is not uncommon in pediatric UTIs. In one previous study, 5.6% of children with UTI developed septicemia [30]. Prematurity and young age represent common risk factors for bacteremia and septicemia, suggesting immunodeficiency as an important predisposing factor. In our study, out of 8 children who have developed bacteremia, 6 and 2 were <1 year and 2 years of age, respectively. However, because of a lack of information, we could not establish the association between prematurity and septicemia.

Limitation

There are various constraints in our investigation. Due to the retrospective study design, we were unable to establish specific relationships, such as the connection between recurrent UTI and preterm, septicemia and risk factors, and other similar correlations. Secondly, the number of Gram-positive bacterial isolates is too low to comment on, and their antibiotic susceptibility results cannot be relied on. Thirdly, there was a lack of relevant data on antibiotic resistance genotyping. Lastly, the study was a single-center study, and hence, to validate our findings, a large multicenter study is recommended.

Conclusion

Urinary tract infections are common in children, with females being more susceptible. Risk factors include congenital malformations, inadequate fluid intake, infrequent urination, and obesity. Uropathogenic *E. coli* is the main cause, and urosepsis is a common associated complication in pediatric age group. Assessing antibiotic susceptibility and providing timely reports helps physicians select appropriate antibiotic for effective UTI management.

Acknowledgement

The authors would like to extend their heartfelt appreciation to Mr. Jayadev Prasad, the IT manager of Sohar Hospital, as well as the entire personnel of the microbiology laboratory for their unwavering assistance in data collection, which was important in the successful completion of this work.

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How to cite this article:

Sannathimmappa MB, Gouda P, Al-Mohana MHJ, Alisaii GKH, Al-Jahwari RJM, Al Maqbali RKA, Aravindakshan R, Al-Risi M, Nambiar V. Risk factors, bacterial profile, and outcomes of urinary tract infection among children treated at a secondary care hospital in Oman. J Krishna Inst Med Sci Univ 2024; 13(2):67-77.

Submitted: *13-Jan-2024* ***Accepted:*** *11-Mar-2024* ***Published:*** *01-Apr-2024*