Original Article

Risk Factors of Urinary Tract Infection Caused by Extended-Spectrum Beta-Lactamases-Producing Bacteria in Children

Dr. Md. Hasan Moshiur Shawon [1] *, Prof. Dr. Shanjoy Kumar Paul [2]

1. Junior Consultant Paediatrics, District Hospital, Pirojpur, Bangladesh.
2. Former Professor & HoD of Paediatric Nephrology, Sir Salimullah Medical College, Dhaka, Bangladesh.

* Correspondence: shawon.sb3@gmail.com

Abstract: Urinary tract infections caused by Extended-spectrum β-lactamases-producing bacteria among children is a therapeutic challenge because it requires broad-spectrum antibiotics for treatment which further increases antimicrobial resistance. World health organisation (WHO) has declared ESBL-producing Enterobacterales as critical priority pathogens. This study determined the risk factors of UTI caused by ESBL-producing bacteria in children and their antibiotic susceptibility pattern. Urine samples were collected using standard aseptic techniques from children who were suspected cases of UTI. Urine culture and bacteria isolation were performed following standard bacteriological techniques. The Kirby-Bauer disk diffusion technique and the Double-disc synergy test were used to investigate antibiotic susceptibility and presence of ESBL production. The most frequently isolated bacteria was E. coli in both ESBL and non-ESBL group. Almost all of the ESBL-producing bacteria were resistant to Cephalosporin group of antibiotics followed by Amoxiclav and Co-trimoxazole. Lowest resistance were found to Colistin followed by Imipenem and Meropenem. The most predominant risk factor for ESBL-UTI in children was history of prior use of antibiotics (OR 8.3, 95% CI (3.8-18.5)) followed by previous hospitalization (OR 2.89, 95% CI (1.3-6.6)) and previous UTI (OR 9.0, 95% CI (1.1-74.2)). However, none of them was found as an independent risk factor. The risk factors for ESBL-UTI and their antibiotic sensitivity pattern identified in this study will be helpful for selection of an appropriate empirical antibiotic while awaiting for urine culture report. ESBL testing need to incorporate in the routine clinical practice and the judicious use of antibiotics should be strengthened to decrease the antimicrobial resistance rate.

Keywords: Extended-Spectrum Beta-Lactamases, Urinary Tract Infections, children, antibiotic resistance

1. INTRODUCTION

Urinary tract infections (UTI) occurs when microorganisms invade and multiply in the urinary tract. Anatomically, UTIs are upper or lower tract infections. Upper tract UTI causes kidney and ureter inflammation (pyelonephritis). This causes abdominal pain, loin tenderness, fever, anorexia, vomiting, lethargy, and malaise [1]. Lower tract UTI causes bladder (cystitis) and urethra infection, causing lower abdominal or suprapubic pain, dysuria, urine frequency, and urgency [2]. Older children may have infection-related symptoms, younger patients often lack these typical indications, making upper and lower UTI difficult to distinguish [3]. The third most prevalent illness in children is UTI, behind respiratory and gastrointestinal infections [4]. Feverish newborns, ill children, and older children with urinary symptoms account for 6%–8% of UTI cases. Peak prevalence occurs in newborns, toddlers, and adolescents [5]. UTI is more likely in female and uncircumcised male babies due to bacterial skin flora concentration under the nappy, shorter female urethral distance, and foreskin surface area [6]. Toddler toilet training can cause volitional holding and bladder stasis, causing UTIs. When sexual activity upsets bacteria at the urethral entrance, prevalence rises in adolescent girls [7]. Due to poor sanitation, living methods, undernourishment, and environmental conditions, this disease is more prevalent in underdeveloped nations. Enterobacterales (previously

called Enterobacteriaceae) are Gram-negative, non-spore-forming, facultative anaerobic bacilli that cause > 80% of UTIs [8]. Escherichia coli is the most common, Klebsiella, Enterobacter, and Proteus spp as well [9]. Other Gram-negative microbes like Pseudomonas aeruginosa can cause UTIs rarely. Enterococcus spp. (patients with a urinary catheter, urinary tract instrumentation, or anatomical abnormality), Staphylococcus saprophyticus (sexually active adolescents), and Streptococcus Group B (neonates) are Gram-positive bacterial pathogens [10]. Children rarely get UTIs from viruses or fungi, save for Candida species in premature neonates. Patients with structural defects may have several organisms [11]. ESBLs, plasmid-mediated β-lactamases, hydrolyze extended-spectrum Cephalosporins (Cefotaxime, Ceftriaxone, and Ceftazidime) and Oxyimino-monobactam (Aztreonam), but not Cephamycins (Cefoxitin and Cefotetan) or Carbapenems (Meropenem and Imipenem). ESBLs transmit resistance to antibiotics and related Oxyimino-β lactams. Clavulanic acid, Sulbactam, and Tazobactam are 'classical' β-lactamase inhibitors that inhibit these enzymes [12]. ESBLs provide Gram-negative bacteria resistance by preventing β-lactams from reaching penicillin binding proteins (PBPs), decreasing affinity for PBPs, and destroying the antibiotic through β-lactamases [13]. The most prevalent resistance mechanism against β-lactam antibiotics is beta-lactamase enzyme synthesis. Because bacteria share mobile genetic components, ESBL enzymes have spread. Clonal development of ESBL-producing bacteria, such as E. coli ST131, which is resistant to quinolones, has caused global epidemics [14]. E. coli and Klebsiella spp. produce ESBLs, but Enterobacter, Proteus, Citrobacter, Morganella, Providencia, Salmonella, and Serratia can also cause dozens of infections. ESBL-related infections are concerning for various reasons. First, multidrug resistance makes them hard to treat (Jacoby, 1997). Second, ESBL infections may delay treatment [15]. Third, ESBL infections cause longer hospital stays and higher expenses, fourth, existing identification approaches may underestimate these organisms' prevalence [16]. Finally, ESBL infections increase the likelihood of clinical failure and death in adults and children. Poor medication regulatory and control systems in many countries have led to antibiotic misuse and overuse in humans and animals [17]. These activities promote the spread of resistant bacterial strains into the community and clinic, lowering treatment outcomes. When infection prevention and management are lacking, drug-resistant pathogenic bacterial strains can spread anywhere [18]. Inappropriate prescribing, patient noncompliance with duration, dose, and frequency of antibiotics, and antibiotic use in livestock and fish farms are known sources of antibiotic resistance. Antibiotic resistance increases in nations where antibiotics are available without a prescription and self-medication is frequent [19]. In places with heavy antibiotic usage regardless of history, antibiotic resistance is more likely [20]. Patients under 15 and over 45 are more susceptible to ESBL, alarmingly, 25% of newborns and young (0–15 year olds) have UTI. Previous antibiotic exposure, UTI, hospitalization, underlying disease, urinary tract abnormalities, and immunosuppressant drug use have been linked to ESBL-positive UTIs in children [21].

2. MATERIALS AND METHODS

The study follow the cross-sectional analytical study design, study place was department of Pediatrics and Department of Microbiology, Sir Salimullah Medical College Mitford Hospital (SSMCMH), Dhaka. On the basis of inclusion & exclusion criteria, all the patients from 01 month to 12 years of age presented to the pediatric outpatient department or admitted to pediatric inpatient ward with clinical feature(s) of UTI (fever, abdominal pain, loin pain, dysuria, frequency, urgency etc.) within the defined period were included. Data has been collected with the help of purposive sampling technique. Sample size was calculated by following formula:

$$n = \left[\frac{Z\alpha\sqrt{2p(100-p)} + Z\beta\sqrt{p_1(100-p_1) + p_2(100-p_2)}}{p_1 - p_2}\right]^2$$

n = the required sample size
p_1 = anticipated probability of exposure among cases
p_2 = anticipated probability of exposure among control

$p = (p_1 + p_2) \div 2$
Z = z- value of SND at a given level of significance
$Z\beta$ = z- value of SND at a given power

Here,

$p_1 = 79$
$p_2 = 52.2$
$p = (79 + 52.2) \div 2$
$= 65.6$
Z = 1.96
$Z\beta$ = 1.28

So calculated sample size:

$$n = \left[\frac{1.96\sqrt{2 \times 65.6(100 - 65.6)} + 1.28\sqrt{79(100 - 79) + 52.2(100 - 52.2)}}{79 - 52.2}\right]^2$$

$$n = \left[\frac{1.96\sqrt{4513.28} + 1.28\sqrt{4154.16}}{26.8}\right]^2$$

$$n = \left[\frac{1.96 \times 67.18 + 1.28 \times 64.45}{26.8}\right]^2$$

$$n = \left[\frac{131.67 + 82.5}{26.8}\right]^2$$

$$n = [7.99]^2$$

$$n = 63.84$$

n = 64

A number of 64 in each group so the total sample (64+64) = 128. Data were collected by interview of the parents or guardians, clinical examination and laboratory investigations using the research instrument. Sociodemographic data including age (years), sex and clinical history of participants such as previous use of antibiotic, previous hospitalization, prior UTI, use of immunosuppressant drug within the past 3 months and associated diseases were recorded. All patients presented to the pediatric outpatient department or admitted to pediatric inpatient ward, SSMCMH, fulfilling the inclusion criteria were enrolled for the study. Glans penis and foreskin in male, while perineum including labia minora and majora in female were cleaned using tap water at room temperature prior to obtaining the urine sample. Freshly voided early morning mid-stream urine (MSU) from children 2 years and older and clean catch or sterile, adhesive urine bag specimen from children younger than 2 years were collected into properly labelled, dry, clean, sterile, transparent, screw-capped, wide-mouth, leak-proof plastic containers. After labeling the container, samples were transported immediately to the Clinical pathology and Microbiology laboratory of SSMC with a requisition form for routine examination and culture & antibiotic susceptibility test. The samples were analyzed and processed according to the standard protocol within 2 hours of collection. Using a calibrated wire loop of loop diameter 4mm, l0 µl of uncentrifuged urine were inoculated into 5% Blood agar and MacConkey agar media (Oxoid Ltd. England). Semi quantitative streaking method was used for quantification of bacterial load in urine. The inoculated plates were incubated at 37^{o}C aerobically, after overnight incubation, plates were examined for growth and colony forming units (cfu) per ml were calculated. A specimen was considered positive for UTI if a single organism was cultured at a concentration of >10^5 cfu/ ml. Pure isolates of bacterial pathogen were preliminarily characterized by their colony morphology and Gram-staining. All positive urine cultures showing significant bacteriuria were further identified by their characteristic appearance on their respective media and confirmed by the pattern of biochemical reaction using the standard procedures. Isolated bacteria were *E. coli, Pseudomonas, Klebsiella, Acinetobacter, Providencia, Morganella, Serratia, Citrobacter* and *Proteus*. A single colony

represents one organism, if an inoculum of 0.01 ml produces 20 colonies, the number of organisms represents in 0.01 ml of urine is 20. So one ml urine contains 2 x 10^3 organisms. A count of 1 x 10^5 or more bacteria per ml of urine were considered as clinically significant [22]. Susceptibility to antimicrobial agents of all isolates were done by Kirby-Bauer modified disk-diffusion technique. Three to five isolated colonies of the organisms to be tested were picked from the pure culture plates by a sterile wire loop and suspended in 5 ml of nutrient broth in a screw capped test tube and mixed gently until it forms a homogenous suspension. In a good light the turbidity of suspension was matched to 0.5 McFarland standards in order to standardize the inoculums density. A sterile cotton swab was dipped into the suspension and the excess were removed by gentle rotation of the swab against the surface of the tube. The swab was then used to distribute the bacteria suspension evenly over the entire surface of Mueller-Hinton agar (Oxoid Ltd. England). The inoculated plates were left on the flat surface at room temperature to dry for 10-15 minutes. Then the antibiotic discs were placed on the inoculated plates. The antibiotics for disk diffusion testing were obtained from Oxoid that include: Amoxicillin (20 µg) + Clavulanic acid (10 µg), Ceftriaxone (30 µg), Ceftazidime (30 µg), Cefotaxime (30 µg), Aztreonam (10 µg), Cefixime (30 µg), Doxycycline (30 µg), Imipenem (10 µg), Meropenem (10 µg), Co-trimoxazole (23.75/1.25 µg), Ciprofloxacin (30 µg), Levofloxacin (5 µg), Gentamicin (10 µg), Amikacin (10 µg), Nitrofurantoin (300µg), Chloramphenicol (30 µg), Tetracycline (30 µg), Nalidixic acid (30 µg) were used to see the sensitivity patterns of the organism. The plates were then incubated at 37^{o}C for 24 hours and reading was taken using a ruler on the underside of the plate measured the diameter of each zone of inhibition in mm. Zone of inhibition produced by each was considered into susceptibility categories namely Susceptible (S), Intermediate (I), and Resistant (R) by CLSI (2015). All the gram-negative isolates were tested for detection of ESBL by Double-Disc Synergy Test (DDST). Antimicrobial discs (Oxoid Ltd. England) Ceftazidime (CAZ) 30 µg, Cefotaxime (CTX) 30 µg, Ceftriaxone (CRO) 30 µg were used. Mueller Hinton agar plates were prepared and inoculated with standardized inoculums of the organism with sterile cotton swab. Disc containing 20 µg Amoxicillin and 10 µg Clavulanic acid was placed in the center of the inoculated plate. Third generation Cephalosporin disc of Ceftazidime, Ceftriaxone and Cefotaxime were placed about 20 mm distant from Amoxicillin-Clavulanate disc. The plate was incubated overnight at 37ºC. Extension of the inhibition zone of Ceftazidime, Ceftriaxone and Cefotaxime disc on the side exposed to the disc containing Amoxicillin and Clavulanic acid was considered positive for ESBLs. Standard strain of *Klebsiella pneumoniae* ATCC 700603 was used as ESBL-positive control and *E. coli* ATCC 25922 was used as ESBL-negative control. All Statistical analyses were done using Statistical Package for Social Science (SPSS) software version 27.0.

3. RESULTS AND DISCUSSION

Data were expressed as frequency and percentage and mean ±SD unpaired student t-test and Chi-square test was done ns = not significant Majority of the patients were age ranges between 1-5 years in both group (p=0.854). There was male predominance in ESBL-UTI group (p=0.596).

Table 01: Age and sex distribution of the patients with ESBL-UTI and non-ESBL-UTI (N=128)

Variables	ESBL (n=64) No. (%)	Non-ESBL (n=64) No. (%)	p-value
Age groups			

1 month-12 months 1 year-5 years 6 years-12 years	15(23.4%) 32(50.0%) 17(26.6%)	13(20.3%) 33(51.6%) 18(28.1%)	0.854^{ns}
Mean±SD Range	3.76±3.41 (0.20-12) years	3.87±3.25 (0.10-12.0) years	
Sex			
Male	34(53.1%)	31(48.4%)	0.596^{ns}
Female	30(46.9%)	33(51.6%)	
Male: Female ratio	1.1:1	1:1.1	

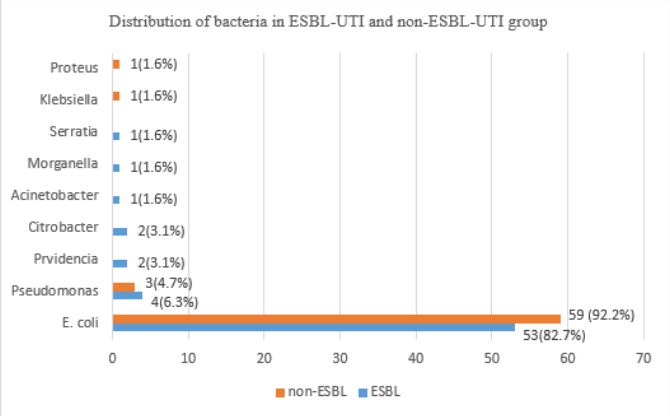

Figure 01: Bar diagram shows distribution of the bacteria in ESBL-UTI and non-ESBL-UTI group.

E. coli was the commonest organism identified in both ESBL-UTI and non-ESBL-UTI group followed by *Pseudomonas*, *Providencia* and others.

Table 02: Antibiotic susceptibility pattern of the isolated bacteria in ESBL-UTI group (n=64)

Antibiotics		Organisms						
		E.coli (n=53)	Pseudomonas (n=4)	Acinetobacter (n=1)	Providencia (n=2)	Citrobacter (n=2)	Morganella (n=1)	Serratia (n=1)
Amoxyclav	S	3(5.7)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)
	R	50(94.3)	4(100.0)	1(100.0)	2(100.0)	1(50.0)	1(100.0)	1(100.0)

Amikacin	S	36(67.9)	4(100.0)	1(100.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
	R	17(32.1)	0(0.0)	0(0.0)	1(50.0)	2(100.0)	1(100.0)	1(100.0)
Aztreonam	S	9(17.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	44(83.0)	3(75.0)	1(100.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Ceftriaxone	S	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	53(100.0)	4(100.0)	0(0.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Cefixime	S	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	53(100.0)	4(100.0)	0(0.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Ceftazidime	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	53(100.0)	4(100.0)	1(100.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Cefotaxime	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	53(100.0)	4(100.0)	1(100.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Cephradine	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	53(100.0)	4(100.0)	1(100.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Ciprofloxacin	S	13(24.5)	3(75.0)	1(100.0)	2(100.0)	1(50.0)	0(0.0)	1(100.0)
	R	40(75.5)	1(25.0)	0(0.0)	0(0.0)	1(50.0)	1(100.0)	0(0.0)
Chloramphenicol	S	32(60.4)	3(75.0)	0(0.0)	0(0.0)	1(50.0)	1(100.0)	0(0.0)
	R	21(39.6)	1(25.0)	1(100.0)	2(100.0)	1(50.0)	0(0.0)	1(100.0)
Co-trimoxazole	S	7(13.2)	1(25.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
	R	46(86.8)	3(75.0)	1(100.0)	1(50.0)	2(100.0)	1(100.0)	1(100.0)
Cefuroxime	S	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	R	53(100.0)	4(100.0)	1(100.0)	2(100.0)	2(100.0)	1(100.0)	1(100.0)
Colistin	S	52(98.1)	4(100.0)	1(100.0)	1(50.0)	2(100.0)	1(100.0)	1(100.0)
	R	1(1.9)	0(0.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
Doxycycline	S	29(54.7)	1(25.0)	1(100.0)	0(0.0)	1(50.0)	1(100.0)	1(100.0)
	R	24(45.3)	3(75.0)	0(0.0)	2(100.0)	1(50.0)	0(0.0)	0(0.0)
Gentamicin	S	28(52.8)	3(75.0)	1(100.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
	R	25(47.2)	1(25.0)	0(0.0)	1(50.0)	2(100.0)	1(100.0)	1(100.0)
Imipenem	S	45(84.9)	4(100.0)	0(0.0)	2(100.0)	0(0.0)	1(100.0)	1(100.0)
	R	8(15.1)	0(0.0)	1(100.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)

Levofloxacin	S	17(32.1)	3(75.0)	1(100.0)	2(100.0)	1(50.0)	0(0.0)	1(100.0)
	R	36(67.9)	1(25.0)	0(0.0)	0(0.0)	1(50.0)	1(100.0)	0(0.0)

Table-2 continued

Table 02: Antibiotic susceptibility pattern of the isolated bacteria in ESBL-UTI group (n=64)

Antibiotic		Organisms						
		E.coli (n=53)	Pseudomonas (n=4)	Acinetobacter (n=1)	Providencia (n=2)	Citrobacter (n=2)	Morganella (n=1)	Serratia (n=1)
Meropenem	S	41(77.4)	4(100.0)	0(0.0)	2(100.0)	0(0.0)	1(100.0)	1(100.0)
	R	12(22.6)	0(0.0)	1(100.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)
Nalidixic acid	S	10(18.9)	2(50.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
	R	43(81.1)	2(50.0)	1(100.0)	1(50.0)	2(100.0)	1(100.0)	1(100.0)
Nitrofurantoin	S	31(58.5)	1(25.0)	1(100.0)	0(0.0)	1(50.0)	0(0.0)	1(100.0)
	R	22(41.5)	3(75.0)	0(0.0)	2(100.0)	1(50.0)	1(100.0)	0(0.0)
Pefloxacin	S	21(39.6)	2(50.0)	1(100.0)	2(100.0)	1(50.0)	0(0.0)	1(100.0)
	R	32(60.4)	2(50.0)	0(0.0)	0(0.0)	1(50.0)	1(100.0)	0(0.0)
Tetracycline	S	40(75.5)	3(75.0)	1(100.0)	0(0.0)	2(100.0)	1(100.0)	0(0.0)
	R	13(24.5)	1(25.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	1(100.0)

Figures in the parentheses indicate corresponding **percentage;**

S=sensitive, R=Resistant, Intermediate was counted as sensitive.

Table 03: Antibiotic susceptibility pattern of the isolated bacteria in non-ESBL-UTI group (n=64)

Antibiotics		**Organisms**			
		E.coli (n=59) No. (%)	**Klebsiella (n=1) No. (%)**	**Proteus (n=1) No. (%)**	**Pseudomonas (n=3) No. (%)**
Amoxyclav	S	38(64.4%)	0(0.0%)	0(0.0%)	0(0.0%)
	R	21(35.6%)	1(100.0%)	1(100.0%)	3(100.0%)
Amikacin	S	58(98.3%)	1(100.0%)	1(100.0%)	3(100.0%)
	R	1(1.7%)	0(0.0%)	0(0.0%)	0(0.0%)

Aztreonam	S	59(100.0%)	1(100.0%)	1(100.0%)	1(33.3%)
	R	0(0.0%)	0(0.0%)	0(0.0%)	2(66.7%)
Ceftriaxone	S	59(100.0%)	1(100.0%)	0(0.0%)	2(66.7%)
	R	0(0.0%)	0(0.0%)	1(100.0%)	1(33.3%)
Cefixime	S	53(89.8%)	1(100.0%)	0(0.0%)	0(0.0%)
	R	6(10.2%)	0(0.0%)	1(100.0%)	3(100.0%)
Ceftazidime	S	59(100.0%)	1(100.0%)	1(100.0%)	3(100.0%)
	R	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Cefotaxime	S	59(100.0%)	1(100.0%)	1(100.0%)	2(66.7%)
	R	0(0.0%)	0(0.0%)	0(0.0%)	1(33.3%)
Cephradine	S	38(64.4%)	0(0.0%)	0(0.0%)	0(0.0%)
	R	21(35.6%)	1(100.0%)	1(100.0%)	3(100.0%)
Ciprofloxacin	S	49(83.1%)	0(0.0%)	0(0.0%)	1(33.3%)
	R	10(16.9%)	1(100.0%)	1(100.0%)	2(66.7%)
Chloramphenicol	S	52(88.1%)	1(100.0%)	1(100.0%)	1(33.3%)
	R	7(11.9%)	0(0.0%)	0(0.0%)	2(66.7%)
Co-trimoxazole	S	27(45.8%)	1(100.0%)	0(0.0%)	0(0.0%)
	R	32(54.2%)	0(0.0%)	1(100.0%)	3(100.0%)
Cefuroxime	S	50(84.7%)	1(100.0%)	1(100.0%)	0(0.0%)
	R	9(15.3%)	0(0.0%)	0(0.0%)	3(100.0%)
Colistin	S	59(100.0%)	1(100.0%)	1(100.0%)	3(100.0%)
	R	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Doxycycline	S	42(71.2%)	1(100.0%)	1(100.0%)	1(33.3%)
	R	17(28.8%)	0(0.0%)	0(0.0%)	2(66.7%)

Table-3 continued

Table 03: Antibiotic susceptibility pattern of the isolated bacteria in non-ESBL-UTI group (n=64)

Antibiotics		Organisms			
		E.coli (n=59) No. (%)	Klebsiella (n=1) No. (%)	Proteus (n=1) No. (%)	Pseudomonas (n=3) No. (%)
Gentamicin	S	46(78.0%)	1(100.0%)	0(0.0%)	2(66.7%)
	R	13(22.0%)	0(0.0%)	1(100.0%)	1(33.3%)
Imipenem	S	59(100.0%)	1(100.0%)	1(100.0%)	1(33.3%)
	R	0(0.0%)	0(0.0%)	0(0.0%)	2(66.7%)

Levofloxacin	S	49(83.1%)	1(100.0%)	0(0.0%)	3(100.0%)
	R	10(16.9%)	0(0.0%)	1(100.0%)	0(0.0%)
Meropenem	S	59(100.0%)	1(100.0%)	1(100.0%)	1(33.3%)
	R	0(0.0%)	0(0.0%)	0(0.0%)	2(66.7%)
Nalidixic acid	S	12(20.3%)	1(100.0%)	1(100.0%)	0(0.0%)
	R	47(79.7%)	0(0.0%)	0(0.0%)	3(100.0%)
Nitrofurantoin	S	46(78.0%)	1(100.0%)	0(0.0%)	0(0.0%)
	R	13(22.0%)	0(0.0%)	1(100.0%)	3(100.0%)
Pefloxacin	S	49(83.1%)	1(100.0%)	0(0.0%)	2(66.7%)
	R	10(16.9%)	0(0.0%)	1(100.0%)	1(33.3%)
Tetracycline	S	49(83.1%)	1(100.0%)	1(100.0%)	3(100.0%)
	R	10(16.9%)	0(0.0%)	0(0.0%)	0(0.0%)

S=sensitive, R=Resistant, Intermediate was counted as sensitive.

Table 04: Pattern of antibiotic resistance between ESBL-UTI and non-ESBL-UTI group (N=128)

Antibiotic	ESBL (n=64) No. (%)	Non-ESBL (n=64) No. (%)	p-value
Amoxiclav	60(93.8%)	26(40.8%)	<0.001[s]
Amikacin	22(34.4%)	1(1.6%)	<0.001[s]
Aztreonam	54(84.4%)	2(3.1%)	<0.001[s]
Ceftriaxone	63(98.4%)	2(3.1%)	<0.001[s]
Cefixime	63(98.4%)	10(15.6%)	<0.001[s]
Ceftazidime	64(100.0%)	0(0.0%)	<0.001[s]
Cefotaxime	64(100.0%)	1(1.6%)	<0.001[s]
Cephradine	64(100.0%)	26(40.6%)	<0.001[s]
Ciprofloxacin	43(67.2%)	14(21.9%)	<0.001[s]
Chloramphenicol	27(42.2%)	9(14.1%)	0.001[s]
Co-trimoxazole	55(85.9%)	36(56.3%)	<0.001[s]
Cefuroxime	64(100.0%)	12(18.8%)	<0.001[s]
Colistin	2(3.1%)	0(0.0%)	0.043[s]
Doxycycline	30(46.9%)	19(29.7%)	0.100[ns]
Gentamicin	31(48.4%)	15(23.4%)	0.002[s]
Imipenem	11(17.2%)	2(3.1%)	0.020[s]
Levofloxacin	39(60.9%)	11(17.2%)	<0.001[s]
Meropenem	15(23.4%)	2(3.1%)	0.002[s]
Nalidixic acid	51(79.7%)	50(78.1%)	0.473[ns]
Nitrofurantoin	29(45.3%)	17(26.6%)	0.007[s]
Pefloxacin	36(56.3%)	12(18.8%)	<0.001[s]
Tetracycline	17(26.6%)	10(15.6%)	0.270[ns]

Chi-square test (χ^2) was done to analyze the data. s= significant, ns = not significant, ESBL-producing bacteria were significantly resistant to commonly used antibiotics.

Table 05: Distribution of the study subjects by Urine examination (N=128)

Urine examination	ESBL (n=64) No. (%)	Non-ESBL (n=64) No. (%)	p-value
Pus cell (per HPF)			
<5	10(15.6%)	8(12.5%)	0.299[ns]
5-10	30(46.8%)	28(43.8%)	
>10	20(31.3%)	18(28.1%)	
Plenty	4(6.3%)	10(15.6%)	
RBC (per HPF)			
<5	54(84.4%)	57(89.1%)	0.927 [ns]
5-10	6(9.4%)	4(6.2%)	
>10	4(6.2%)	3(4.7%)	
Ep cell (per HPF)			
<5	59(92.2%)	60(93.8%)	0.193 [ns]
5-10	5(7.8%)	2(3.1%)	
>10	0(0.0%)	2(3.1%)	
Albumin			
Nil	25(39.1%)	24(37.5%)	0.555 [ns]
Trace	8(12.5%)	14(21.9%)	
1+	8(12.5%)	5(7.8%)	
2+	5(7.8%)	4(6.2%)	
3+	18(28.1%)	17(26.6%)	
pH			
<5	3(4.7%)	0(0.0%)	0.080 [ns]
>5	61(95.3%)	64(100.0%)	
Specific gravity			
1.0-1.015	8(12.5%)	3(4.7%)	0.115 [ns]
1.020-1.030	56(87.5%)	61(95.3%)	
Nephrotic range proteinuria	21(32.8%)	15(23.4%)	0.555 [ns]

Chi-square test (χ^2) was done to analyze the data., s= significant, ns = not significant

None of the urinary findings were statistically significant between two groups.

Table 06: Possible risk factors of study population (N=128)

Possible risk factors	ESBL (n=64) No. (%)	Non-ESBL (n=64) No. (%)	OR (95% CI)	p-value
Previous hospitalization	24(37.5%)	11(17.2%)	2.89 (1.3-6.6)	0.010[s]
H/O previous UTI	8(12.5%)	1(1.6%)	9.0 (1.1-74.2)	0.016 [s]
Previous use of antibiotics	46(71.9%)	15(23.4%)	8.3 (3.8-18.5)	<0.001 [s]
First generation cephalosporin	2(3.1%)	6(9.4%)	0.38 (0.07-2.04)	0.144[ns]
Second generation cephalosporin	2(3.1%)	1(1.6%)	2.03 (0.18-22.9)	0.559 [ns]
Third generation cephalosporin	43(67.2%)	10(15.6%)	11.1 (4.7-25.9)	<0.001[s]
Fourth generation cephalosporin	4(6.3%)	0(0.0%)	-	0.042[s]
Immunosuppressant drug	10(15.6%)	3(4.7%)	3.8 (0.98-14.4)	0.041[s]
Associated diseases	25(39.1%)	16(25%)	1.92(-2.2-30.4)	0.66 [ns]
Uncircumcised boys	30(88.2%)	26(83.9%)	1.44(-7.92-16.52)	0.611[ns]

Odds ratio (OR) with 95% CI and Chi-square test were done to analyze the data, s=significant, ns = not significant

Some patient had history of previous use of more than one generation of antibiotics. Previous hospitalization, H/O previous UTI and previous use of antibiotics (third generation Cephalosporin) were found as risk factors for ESBL-UTI.

Table 07: Independent risk factors for ESBL-positive UTI

	p-value	OR	95% C.I	
			Lower	Upper
Previous hospitalization	.750	.826	.255	2.675

	H/O previous UTI	.320	.308	.030	3.140
	Previous use of antibiotic	.596	.646	.129	3.242
	Third generation cephalosporin	.270	.156	.030	1.808
	Constant	.000	2.840		

Multivariate binary logistic regression analysis was done, where none of them was found as an independent risk factor for ESBL-UTI. E. coli was the most isolated organism in both the ESBL-UTI (84.4%) and non-ESBL-UTI (92.2%) groups. E. coli was the most commonly isolated bacteria in UTI patients by Afroz, Albaramki, Alim, Awean, Islam, Kim, Yang, and Kim, Rahman, and Topaloglu. High E. coli ratios cause autoinfection since the bacteria are in the feces. E. coli can also create a biofilm on the bladder wall that resists the immune system. This study found that Pseudomonas caused 6.3% of ESBL-UTI and 4.7% of non-ESBL-UTI. Pseudomonas as the second main cause of UTI. Klebsiella was the second biggest cause and a major risk factor for ESBL development in other investigations. Different environmental circumstances, host characteristics, healthcare and education programs, socioeconomic levels, and cleanliness practices in each nation may affect uropathogen kind and distribution. The ESBL-UTI group had a considerably greater rate of AMR than the non-ESBL-UTI group. ALL ESBL isolates were resistant to Ceftazidime, Cefotaxime, and Cefuroxime, followed by Ceftriaxone, Cefixime, Amoxiclav, and Co-trimoxazole (p< Colistin, Imipenem, and Meropenem had the lowest resistance.

3.2 Discussion

A study found that all ESBL isolates were resistant to cefuroxime, ceftazidime, and cefotaxime and 99% to ampicillin and ceftriaxone. All isolates were sensitive to Meropenem, Imipenem, and Colistin, regardless of ESBL status [23]. ESBL E. coli in India exhibited high resistance to third-generation cephalosporins, quinolones, and co-trimoxazole, but less resistance to Gentamicin, Levofloxacin, Nitrofurantoin, Netilmicin, and Imipenem [24]. All ESBL isolates in a Finnish study were resistant to Cephalosporins and susceptible to Meropenem. ESBL-producing bacteria showed increased resistance to non-β-lactam antibiotics, such as Trimethoprim (76%), Norfloxacin (33%), and Sulphatrimethoprim (76%) [25]. The only clinically meaningful Trimethoprim resistance in ESBL-negative bacteria was 27%. In our country, oral third-generation antibiotics like Cefixime are overprescribed [26]. Through antibiotic selection pressure (ESBLs), this method may increase gram-negative bacteria drug resistance. In this study, 50% of ESBL-UTI children were 1–5 years old [27]. A recent study found more UTIs among 1-5-year-olds, and most instances are over 2 [28]. ESBL-UTI risk was independent for children under one year old, a CMH, Dhaka study found that UTIs were more common in children under 5 (62.5%) [29]. Possibly because younger children aren't toilet-trained. Fecal flora ascending infection is more common in this age range [30]. In this study, ESBL-UTI members were mostly men (1.1:1), but not significantly so (p=0.596), a study found no gender correlation however several research have linked male sex to risk factors [31]. Other research indicated female predominance, as females are more likely to get UTIs [32]. Short urethras and other factors may make this condition more common in girls. In early infancy, boys are more prone to congenital deformity, but as they get older, the gender ratio reversesd [33]. Physician visit preferences may explain male predominance in UTI. Significant risk factors reported in this study by univariate analysis include prior antibiotic use (p<0.001), past UTI (p=0.016), and prior hospitalization (p=0.010). Children with antibiotic history had 8.3 times the risk of ESBL-UTI. Third-generation Cephalosporin was 11 times riskier. Different trials show different effects with prior antibiotic use, multiple studies indicated that antibiotic use was an independent risk factor for ESBL-UTI [34]. Penicillin, second- and third-generation Cephalosporin, Quinolones, Carbapenems, and Aminoglycosides, and suppression treatment (TMP/SMX, Nitrofurantoin) were risk factors for

ESBL-UTI [35]. Previous antibiotic therapy did not increase the risk of ESBL-UTI in children [36]. In a meta-analysis of five investigations, uropathogens from children who had taken antibiotics were more than 10 times more likely to be resistant. It increased risk may last up to six months after antibiotic treatment, It also found that restricting third-generation Cephalosporins can suppress ESBL-producing bacteria in hospitals [37]. Children with a 3-month hospitalization history had a 3-fold higher risk of ESBL-UTI, findings showed that hospitalization within 3 months was an independent risk factor for ESBL-UTI in children [38]. Children may acquire ESBL-producing bacteria via healthcare processes and become reservoirs for them. Returning to the community may cause ESBL-UTI [39]. In this study, previous UTI in the recent 3 months increased ESBL-UTI risk by 9 times and [40] support this finding as well. However, [41] observed that children having a history of UTI within 12 months were less likely to contract ESBL-producing Enterobacteriacea. Multiple hospital stays and broad-spectrum antibiotics may generate ESBL-producing bacteria [42]. None were independent risk factors for ESBL-UTI in children on multivariate binary logistic regression, [44] supported this finding. A retrospective Korean investigation found no risk factors in up to 60% of babies with community-acquired ESBL-producing uropathogens [45].

4. CONCLUSIONS

The Pediatrics and Microbiology departments of Sir Salimullah Medical College Mitford Hospital in Dhaka conducted a cross-sectional study to investigate the risk factors for urinary tract infections caused by ESBL-producing bacteria in children ranging in age from one month to twelve years based on the results of the study. In both the ESBL-UTI (84.4%) and the non-ESBL-UTI (92.2%) groups, E. coli was the bacterium that became the most isolated. As far as Afroz, Albaramki, Alim, Awean, Islam, Kim, Yang, and Kim, Rahman, and Topaloglu were concerned, the bacteria that was most frequently isolated from UTI patients was E. coli. Due to the fact that the bacteria are present in the feces, high E. coli ratios might lead to autoinfection. E. coli has the ability to produce a biofilm on the bladder wall that is resistant to the immune system. According to the findings of this investigation, Pseudomonas was responsible for 6.3% of ESBL-UTI and 4.7% of non-ESBL-UTI. Pseudomonas was the second most common cause of urinary tract infections (UTIs). According to the findings of earlier investigations, Klebsiella was the second most significant cause and a significant risk factor for the development of ESBL. There are a variety of factors that can influence the type of uropathogen and its dissemination, including the environment, the features of the host, the healthcare and education programs, the socioeconomic levels, and the cleaning practices of each nation. The ESBL-UTI group had an antimicrobial resistance rate that was much higher than the non-ESBL-UTI group's rate. There was a high level of resistance among all ESBL isolates to Ceftazidime, Cefotaxime, and Cefuroxime. The next most resistant isolates were Ceftriaxone, Cefixime, Amoxiclav, and Co-trimoxazole (p< Colistin, Imipenem, and Meropenem). E. coli was the most prevalent of the uropathogens that were isolated, and this was true for both the ESBL and the non-ESBL-UTI groups. The Cephalosporin group of antibiotics was ineffective against almost all of the ESBL-producing bacteria, followed by Amoxiclav and Co-trimoxazole as the most effective antibiotics. Colistin emerged as the antibiotic with the least amount of resistance, followed by imipenem and meropenem. Prior hospitalization and a history of urinary tract infections were the two most important risk factors for urinary tract infections (UTIs) caused by ESBL-producing bacteria. The most prominent risk factor was a history of antibiotic use in the past. An independent risk factor for ESBL-positive urinary tract infections was not discovered in any of them. During the process of selecting a suitable empirical therapy, the risk factors and antibiotic susceptibility pattern that were discovered in this study will be of great assistance.It is recommended that ESBL testing be incorporated into the standard clinical practice. It is important for clinicians to use caution while administering antibiotics.

REFERENCES

[1] Tullus, K., & Shaikh, N. (2020). Urinary tract infections in children. The Lancet, 395(10237), 1659-1668.
[2] Mattoo, T. K., Shaikh, N., & Nelson, C. P. (2021). Contemporary management of urinary tract infection in children. Pediatrics, 147(2).
[3] A't Hoen, L., Bogaert, G., Radmayr, C., Dogan, H. S., Nijman, R. J., Quaedackers, J., ... & Stein, R. (2021). Update of the EAU/ESPU guidelines on urinary tract infections in children. Journal of pediatric urology, 17(2), 200-207.

[4] Kaur, R., & Kaur, R. (2021). Symptoms, risk factors, diagnosis and treatment of urinary tract infections. Postgraduate medical journal, 97(1154), 803-812.
[5] Khan, Muhammad & Ahmed, Tauseef & Mahmood, Asad & Munir, Nadia & Warraich, Usman & Haque, Arifa & Zulfiqar, Rabia. (2024). THE CYTOTOXIC CONSEQUENCES OF SEVERAL TOPICALLY APPLIED GELS COMPRISING HYALURONIC ACID (HA) ON ORAL MICROORGANISMS AND GINGIVAL FIBROBLASTS. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery. 55. 1447-1455.
[6] Lee, A. C., Mullany, L. C., Koffi, A. K., Rafiqullah, I., Khanam, R., Folger, L. V., ... & Baqui, A. H. (2020). Urinary tract infections in pregnancy in a rural population of Bangladesh: population-based prevalence, risk factors, etiology, and antibiotic resistance. BMC Pregnancy and Childbirth, 20, 1-11.
[7] Hidayati, S. F., Umboh, V., & Rondonuwu, S. H. (2022). Relationship between Nutritional Status and Urinary Tract Infection in Children. e-CliniC, 10(2), 288-297.
[8] Weese, J. S., Blondeau, J., Boothe, D., Guardabassi, L. G., Gumleyg, N., Papichh, M., ... & Sykes, J. (2021). International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats. Journal of Japanese Association of Veterinary Nephrology and Urology, 13(1), 46-63.
[9] Larramendy, S., Deglaire, V., Dusollier, P., Fournier, J. P., Caillon, J., Beaudeau, F., & Moret, L. (2020). Risk factors of extended-spectrum beta-lactamases-producing Escherichia coli community acquired urinary tract infections: a systematic review. Infection and Drug Resistance, 3945-3955.
[10] Ammenti, A., Alberici, I., Brugnara, M., Chimenz, R., Guarino, S., La Manna, A., ... & Italian Society of Pediatric Nephrology. (2020). Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatrica, 109(2), 236-247.
[11] Ylinen, E., Salmenlinna, S., Halkilahti, J., Jahnukainen, T., Korhonen, L., Virkkala, T., ... & Saxén, H. (2020). Hemolytic uremic syndrome caused by Shiga toxin–producing Escherichia coli in children: incidence, risk factors, and clinical outcome. Pediatric Nephrology, 35, 1749-1759.
[12] Shamiul Bashir Plabon & Shuvo Horel (2023). Prevalence of Micronutrients Deficiency Diseases and its Improvement Practices in Population of Mohammadpur, Dhaka, Bangladesh. Dinkum Journal of Medical Innovations, 2(10):411-417.
[13] Riaz, Mariam & Javed, Maham & Bukhari, Saima & Shaheen, Faiza & Khan, Tariq & Khalid, Henna & Zulfiqar, Rabia. (2024). BLOODSTREAM INFECTIONS AND TRENDS OF ANTIMICROBIAL SENSITIVITY PATTERN: A LABORATORY BASED STUDY. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery. 55. 1421-1428.
[14] Alhifthy, E. H., Habib, L., Al-Makarem, A. A., AlGhamdi, M., Alsultan, D., Aldhamer, F., ... & Zadah, M. H. (2020). Prevalence of nocturnal enuresis among Saudi children population. Cureus, 12(1).
[15] Bunduki, G. K., Heinz, E., Phiri, V. S., Noah, P., Feasey, N., & Musaya, J. (2021). Virulence factors and antimicrobial resistance of uropathogenic Escherichia coli (UPEC) isolated from urinary tract infections: a systematic review and meta-analysis. BMC infectious diseases, 21, 1-13.
[16] Czajkowski, K., Broś-Konopielko, M., & Teliga-Czajkowska, J. (2021). Urinary tract infection in women. Menopause Review/Przegląd Menopauzalny, 20(1), 40-47.
[17] Czajkowski, K., Broś-Konopielko, M., & Teliga-Czajkowska, J. (2021). Urinary tract infection in women. Menopause Review/Przegląd Menopauzalny, 20(1), 40-47.
[18] Riaz, Mariam & Jadoon, Sara & Khalid, Henna & Khan, Abdul & Khan, Tariq & Mehnaz, Gul & Zulfiqar, Rabia. (2024). The abundance of ESBL-expressing, multidrug- resistant Escherichia coli in Pakistani patients with urinary tract infections. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery. 55. 1347-1356.
[19] Behzadi, P., Urbán, E., Matuz, M., Benkő, R., & Gajdács, M. (2021). The role of gram-negative bacteria in urinary tract infections: current concepts and therapeutic options. Advances in Microbiology, Infectious Diseases and Public Health: Volume 15, 35-69.
[20] Meštrović, T., Matijašić, M., Perić, M., Čipčić Paljetak, H., Barešić, A., & Verbanac, D. (2020). The role of gut, vaginal, and urinary microbiome in urinary tract infections: from bench to bedside. Diagnostics, 11(1), 7.
[21] Lagan, N., Huggard, D., Mc Grane, F., Leahy, T. R., Franklin, O., Roche, E., ... & Molloy, E. J. (2020). Multiorgan involvement and management in children with Down syndrome. Acta Paediatrica, 109(6), 1096-1111.

[22] Mutahira, Ayesha & Aishi, Shamima & Ahmad, Fozan & Firas, Noor & Al-Kahachi, Qays & Zulfiqar, Rabia & Qasim, Muhammad Bilal & Aman, Aunima. (2024). AN INVESTIGATION OF COMMON AND DISEASE-SPECIFIC HOST GENE EXPRESSION- MICROBIOME CORRELATIONS AMONG HUMAN DISORDERS: LABORATORY BASED EXPERIMENTAL STUDY. Chinese Science Bulletin. 69. 993-1004.

[23] A't Hoen, L., Bogaert, G., Radmayr, C., Dogan, H. S., Nijman, R. J., Quaedackers, J., ... & Stein, R. (2021). Update of the EAU/ESPU guidelines on urinary tract infections in children. Journal of pediatric urology, 17(2), 200-207.

[24] Czajkowski, K., Broś-Konopielko, M., & Teliga-Czajkowska, J. (2021). Urinary tract infection in women. Menopause Review/Przegląd Menopauzalny, 20(1), 40-47.

[25] Belete, M. A., & Saravanan, M. (2020). A systematic review on drug resistant urinary tract infection among pregnant women in developing countries in Africa and Asia; 2005–2016. Infection and drug resistance, 1465-1477.

[26] Mattoo, T. K., Shaikh, N., & Nelson, C. P. (2021). Contemporary management of urinary tract infection in children. Pediatrics, 147(2).

[27] Wagenlehner, F. M., Bjerklund Johansen, T. E., Cai, T., Koves, B., Kranz, J., Pilatz, A., & Tandogdu, Z. (2020). Epidemiology, definition and treatment of complicated urinary tract infections. Nature Reviews Urology, 17(10), 586-600.

[28] Nimra Naseem, Rubab Zahra, Umm-e-Aimen & Tahir Rana (2023). Literature Review on Comparison of the effect of Single Oral Dose 150 Mg Pregabalin Premedication to Single Oral Dose 100mg Tramadol in Elective Inguinal Hernia Surgery. Dinkum Journal of Medical Innovations, 2(01):01-11.

[29] Bunduki, G. K., Heinz, E., Phiri, V. S., Noah, P., Feasey, N., & Musaya, J. (2021). Virulence factors and antimicrobial resistance of uropathogenic Escherichia coli (UPEC) isolated from urinary tract infections: a systematic review and meta-analysis. BMC infectious diseases, 21, 1-13.

[30] Yamanouchi, S., Kimata, T., Akagawa, Y., Akagawa, S., Kino, J., Tsuji, S., & Kaneko, K. (2021). Reduced urinary excretion of neutrophil gelatinase-associated lipocalin as a risk factor for recurrence of febrile urinary tract infection in children. Pediatric Nephrology, 36, 1473-1479.

[31] Oliveira, E. A., & Mak, R. H. (2020). Urinary tract infection in pediatrics: an overview. Jornal de pediatria, 96, 65-79.

[32] Huang, L., Huang, C., Yan, Y., Sun, L., & Li, H. (2022). Urinary tract infection etiological profiles and antibiotic resistance patterns varied among different age categories: a retrospective study from a tertiary general hospital during a 12-year period. Frontiers in microbiology, 12, 813145.

[33] Ammenti, A., Alberici, I., Brugnara, M., Chimenz, R., Guarino, S., La Manna, A., ... & Italian Society of Pediatric Nephrology. (2020). Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatrica, 109(2), 236-247.

[34] Allen, S. R. (2021). Urinary tract infections in pregnancy. In Clinical Maternal-Fetal Medicine (pp. 77-1). CRC Press.

[35] Tullus, K., & Shaikh, N. (2020). Urinary tract infections in children. The Lancet, 395(10237), 1659-1668.

[36] Meštrović, T., Matijašić, M., Perić, M., Čipčić Paljetak, H., Barešić, A., & Verbanac, D. (2020). The role of gut, vaginal, and urinary microbiome in urinary tract infections: from bench to bedside. Diagnostics, 11(1), 7.

[37] Nabeela Riaz, Rabia Zulfiqar, Muhammad Naveed Akhter & Msooma Sheikh (2023). Dentinogenesis Imperfecta type II Underwent Whole Mouth Rehabilitation Employing Various Treatment Modalities. Dinkum Journal of Medical Innovations, 2(06):201-206.

[38] Dmitri Krysko & Ume e Aimen (2023). Literature Review on Struggle of Guardians in Administration of Medicine in Children. Dinkum Journal of Medical Innovations, 2(09):338-344.

[39] Klein, R. D., & Hultgren, S. J. (2020). Urinary tract infections: microbial pathogenesis, host–pathogen interactions and new treatment strategies. Nature Reviews Microbiology, 18(4), 211-226.

[40] Bader, M. S., Loeb, M., Leto, D., & Brooks, A. A. (2020). Treatment of urinary tract infections in the era of antimicrobial resistance and new antimicrobial agents. Postgraduate medicine, 132(3), 234-250.

[41] Lenger, S. M., Bradley, M. S., Thomas, D. A., Bertolet, M. H., Lowder, J. L., & Sutcliffe, S. (2020). D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. American journal of obstetrics and gynecology, 223(2), 265-e1.

[42] González de Llano, D., Moreno-Arribas, M. V., & Bartolomé, B. (2020). Cranberry polyphenols and prevention against urinary tract infections: relevant considerations. Molecules, 25(15), 3523.

[43] Vazouras, K., Velali, K., Tassiou, I., Anastasiou-Katsiardani, A., Athanasopoulou, K., Barbouni, A., ... & Hsia, Y. (2020). Antibiotic treatment and antimicrobial resistance in children with urinary tract infections. Journal of global antimicrobial resistance, 20, 4-10.

[44] Neugent, M. L., Hulyalkar, N. V., Nguyen, V. H., Zimmern, P. E., & De Nisco, N. J. (2020). Advances in understanding the human urinary microbiome and its potential role in urinary tract infection. MBio, 11(2), 10-1128.

[45] Ginsberg, D. A., Boone, T. B., Cameron, A. P., Gousse, A., Kaufman, M. R., Keays, E., ... & Kraus, S. R. (2021). The AUA/SUFU guideline on adult neurogenic lower urinary tract dysfunction: diagnosis and evaluation. The Journal of Urology, 206(5), 1097-1105.

