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PEDIATRIC RISK FACTORS AND CHARACTERISTICS OF URINARY TRACT INFECTIONS CAUSED BY ESBL VERSUS NON ESBL ORGANISMS AT MAKASSED GENERAL HOSPITAL

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ABSTRACT

Background: Urinary tract infections (UTIs) are among the most common infectious diseases in pediatrics encountered in the community and in the hospital. Resistance to antibiotics in members of Gram-negative Enterobacteriaceae rose tremendously; highlighted by the emergence of extended spectrum beta-lactamase (ESBL) producing organisms. The incidence of community-onset UTIs caused by ESBL-producing E. coli in children is increasing and the previous use of antibiotics was considered a major risk factor. **Objectives:** To determine the risk factors of community-onset UTIs caused by ESBL-producing E. coli in children**,** study the difference in presentation and laboratory with radiologic findings with those who have non ESBL isolates UTI, and to assess the rate and antibiotics susceptibility of the ESBL isolates. **Methods:** A retrospective cross-sectional study was conducted at Makassed General Hospital in Beirut. Subjects were identified by the following ICD-10 discharge codes: "Urinary tract infection", "Cystitis", and "Pyelonephritis." Children between 1 month and 18 years of age admitted for UTI between January 1st, 2012 and December 31st, 2017 were included. Cases whose urine culture result did not meet our definition for UTI or showed no growth and patients who had long stay at hospital were excluded. **Results:** During the study period, 292 charts have been reviewed, 14 patients were excluded, the remaining 278 were divided into 2 groups; ESBL (103 cases) and non ESBL (175 cases) isolated pathogens with a female predominance (85%). Vesico-ureteral reflux and previous antibiotics use with recent hospitalization and recurrent UTI were found to be independent risk factors for ESBL-producing *E. coli* and *Klebsiella* spp. ($p < 0.05$). Presenting fever was found most common in non ESBL group compared to ESBL (72.3% vs. 56.3% respectively; p-value=0.008), in contrast to dysuria which was more common in ESBL group (35.9% vs. 20.3%; p-value=0.005). Laboratory and radiologic findings showed no statistical significance, however advanced VUR was related to ESBL isolates. The proportions of ESBL-producing organisms causing UTI were increasing and they doubled over the study period (50%). A significant resistance to monobactam with cephalosporins and Bactrim was found >50%, however a complete sensitivity to carbapenems in ESBL pathogens is present. **Conclusion:** The recognition of risk factors for infection with ESBL-producing organisms and the observation of increasing resistance to antibiotics warrant further studies that might lead to new recommendations to guide management of UTIs and antibiotic use in children and adolescents.

KEYWORDS: Urinary tract infections, *E. coli* and *Klebsiella* spp.

INTRODUCTION

Urinary tract infection (UTI) is the second most common infection in children. Recurrent UTI, especially in association with vesico-ureteral reflux (VUR), may lead to long-term sequel such as renal scar, hypertension or end-stage renal disease. They result in high rates of morbidity and high economic costs associated with treatment.[2] Over the last two decades, the resistance to antibiotics in members of Gram-negative Enterobacteriaceae rose tremendously worldwide; highlighted by the emergence of extended spectrum beta-lactamase (ESBL) producing organisms.[1]

ESBL is one of the resistance mechanisms developed by MDR rods to antibiotics. Under this term different enzyme's families are classically gathered: they all can hydrolyze the B-lactam ring, resulting in bacterial resistance to early generation and extended spectrum cephalosporins (*e.g.*, ceftriaxone and ceftazidime), monobactams, and penicillins.[3] Although ESBL-producing (ESBL+) microorganisms emerged as a cause of nosocomial infection in hospitals, community-acquired infections (especially urinary infections) have become a problem with an increasing incidence in clinical practice. The prevalence and distribution of

ESBL+ microorganisms as a cause of community-acquired febrile urinary tract infection/acute pyelonephritis (UTI/APN) in children are not well known and are concerning due to the resistance of these isolates to many beta-lactam antibiotics and other antimicrobials.[2,3,11]

Few recent studies showed that previous use of antibiotics and underlying diseases such as neurological diseases, failure to thrive, and developmental delay were found to be associated with such infection in children. In Lebanon few studies have been done taking in details the specificity and characteristics of the disease.[1,14]

Accordingly, the aim of this study is to determine the risk factors of community-onset UTIs caused by ESBL-producing E. coli in children in Lebanon, study the difference in presentation and laboratory with radiologic findings with those who have non ESBL isolates UTI and to assess the rate and antibiotics susceptibility of the ESBL isolates.

METHODS

This retrospective study was conducted at Makassed General Hospital in Beirut following the approval of the Institutional Review Board. Medical charts were reviewed by examining the following ICD-10 codes for discharge diagnosis: "Urinary tract infection," "Cystitis," and "Pyelonephritis." Children aged between 1 month and 18 years with one of the above discharge diagnosis admitted to the hospital between January 1st, 2012 and December 31st, 2017 and meet the definition of UTI by AAP 2011/2016 were included in the study. Exclusion criteria were: long care stay at hospital, recovered isolates after 72 hours of hospitalization and no growth in urine culture.

Accordingly, to establish the diagnosis of UTI, clinicians should require both urine analysis results that suggest infection (pyuria and/ or bacteriuria) and the presence of at least 50 000 colony-forming units (cfu) per milliliter of a uropathogen cultured from a urine specimen obtained through transurethral catheterization for females and clean catch for males. All decisions regarding the antibiotic therapy were made by the attending physicians who took care of the patients. The initial antibiotic regimen was administered after blood and urine samples had been taken for culture.

Data collected from medical charts included the following: basic demographics (age, gender), hospital stay information (ICU/regular floor admission, length of stay), past medical history (underlying diseases, genitourinary disorders, immunosuppression), previous antibiotic use, recent hospitalizations, past surgical history, method of urine collection, laboratory information (urinalysis, urine culture, antimicrobial susceptibility patterns, complete blood count, basic metabolic panel), imaging results, clinical course and outcomes. The statistical package for social sciences (SPSS version 24) was used for data management and analyses. Categorical variables were compared using Chi square test whereas continuous ones were compared using the student's t –test. A P- value of <0.05 was used to indicate statistical significance.

RESULTS

Table. 1: Patients' demographic characteristics.

	ESBL	Non ESBL	P-value
Age	3.3 (3.4)	4.1 (4.1)	0.13
Gender			
Male	15 (14.6%)	31 (18.2%)	0.43
Female	88 (85.4%)	139 (81.8%)	
Nationality			
Lebanese	88 (85.4%)	152 (89.4%)	0.33
Non-Lebanese	15 (14.6%)	18 (10.6%)	
Pathogens isolated			
E.coli	0 (0.0%)	110 (64.7%)	<0.0001
E esbl	91 (88.4%)	0 (0.0%)	
Klebsiella	0 (0.0%)	13 (7.7%)	
K esbl	12 (11.7%)	0 (0.0%)	
Proteus	0 (0.0%)	11 (6.5%)	
Others	0 (0.0%)	36 (21.2%)	

Table. 2: Radiologic results.

variables	ESBL	Non ESBL	P-value
Ultrasound results			
Normal	66 (72.5%)	98 (68.5%)	
Positive findings	25 (27.5%)	45 (31.5%)	0.52
VCUG			
Normal	20 (71.4%)	22 (73.3%)	
Positive VUR	8 (28.6%)	8 (26.7%)	0.87

Table. 3: Analysis of clinical features of UTI.

variables	ESBL	Non ESBL	P-value
Febrile duration (d)	1.78 (2.58)	1.91 (1.77)	0.65
Fever	58 (56.3%)	123 (72.4%)	0.007
Dysuria	37 (35.9%)	37 (21.9%)	0.012
Abdominal pain	32 (31.1)	51 (30.2%)	0.88
Frequency/urgency	19 (18.5%)	28 (16.6%)	0.69
Other symptoms	39 (37.9%)	86 (50.6%)	0.04
Length of Saty	8.82 (5.07)	5.80 (4.15)	<0.0001
Hemoglobin	10.8 (1.3)	11.3 (1.6)	0.01
WBC	13.2 (5.9)	14.2 (6.7)	0.25
Neutrophils	50.1 (18.0)	60.7 (19.1)	<0.0001
Bands	0.59 (1.90)	0.86 (3.80)	0.44
Platelets	386.1 (140.3)	367.1 (152.2)	0.31
CRP	6.5 (9.3)	6.5 (7.6)	0.98
BUN	9.1 (3.9)	10.0 (4.5)	0.11
Creatinine	0.36 (0.45)	0.34 (0.18)	0.74
Urine leukococyte esterase Normal (0-2) Positive (3-5)	 74 (71.8%) 29 (28.2%)	 127 (74.7%) 43 (25.3%)	 0.60
Urine nitrite Positive Negative	 36 (35.0%) 67 (65.1%)	 62 (36.5%) 108 (63.5%)	 0.80
Urine WBC	7.78 (4.84%)	7.35 (5.06%)	0.49
Radio ultrasound Negative Positive	 66 (72.5%) 25 (27.5%)	 98 (68.5) 45 (31.5%)	 0.52

Table. 4: Risk factors.

Risk factors	ESBL	Non ESBL	P-value
Systemic diseases	18 (17.5%)	34 (20.0%)	0.61
Renal disease	8 (7.8%)	8 (4.7%)	0.30
Posterior urethral valve	0 (0.0%)	1 (0.6%)	1.00
Vesico urinary reflux	13 (12.6%)	11 (6.5%)	0.08
Recurrent UTI	42 (40.8%)	39 (22.9%)	0.002
Genitourinary surgery	8 (7.8%)	7 (4.1%)	0.20
Circumcision	9 (56.3%)	15 (41.7%)	0.33
Constipation	17 (16.5%)	28 (16.5%)	0.99
Non GU surgery	8 (7.8%)	2 (1.2%)	0.005
Immunocompromised	6 (5.8%)	5 (2.9%)	0.34
Failure to thrive	11 (10.7%)	15 (8.8%)	0.61
Previous antibiotics use	42 (40.8%)	34 (20.0%)	<0.0001
Recent hospitalization within one month	22 (21.4%)	17 (10.0%)	0.009
None	30 (29.1%)	75 (44.1%)	0.01

Table 5: Antimicrobial sensitivity to ESBL and isolates

Antibiotic	Sensitive	Resistant
Amikacin	241 (93.4%)	17 (6.6%)
Cefepime	240 (93.0%)	18 (7.0%)
Ciprofloxacin	254 (98.5%)	4 (1.5%)
Ertapenem	258 (100.0%)	0 (0.0%)
Fosfomycin	245 (95.0%)	13 (5.0%)
Gentamicin	240 (93.0%)	18 (7.0%)
Imipenem	258 (100.0%)	0 (0.0%)
Nitrofurantoin	234 (90.7%)	24 (9.3%)
Tigecycline	197 (76.4%)	61 (23.6%)
Amoxicilin	43 (16.7%)	215 (83.3%)
Ampicillin	56 (21.7%)	202 (78.3%)

Aztreonam	133 (51.6%)	125 (48.5%)
Ceftazidime	143 (55.4%)	115 (44.6%)
Ceftriaxone	137 (53.1%)	121 (46.9%)
Cefuroxime	130 (50.4%)	128 (49.6%)
Bactrim	125 (48.5%)	133 (51.6%)

Table. 6: Antibiotics used for treatment.

Antibiotics used	ESBL	Non ESBL	P-value
Carbapenem	76 (76.8%)	6 (3.7%)	<0.0001
3rd generation cephalosporin	13 (13.1%)	138 (84.7%)	
4th generation cephalosporin	1 (1.0%)	7 (4.3%)	
Others	9 (9.1%)	12 (7.4%)	

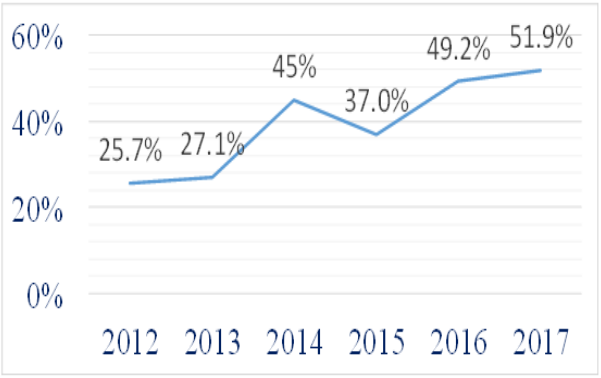

Figure. 1: Trend showing percentage of UTI caused by ESBL.

During the study period, 292 charts have been reviewed, 5 were been excluded because they did not meet the definition of UTI according to the American Academy of Pediatrics guidelines 2011/2016, 2 had long stay in hospital, 2 mortalities because of urosepsis and 5 charts could not be retrieved. The remaining cases were reviewed and 278 cases were included for analysis. They have been divided into 2 groups ESBL (103 cases, 37.1%) and non ESBL (175, 62.9% cases) isolated pathogens.

Patients in ESBL group were younger than those in non ESBL group with mean age 3.4 and 4.1 years respectively but they were not statistically significant different (P-value= 0.13). Overall, females were predominant in both group >80 %. The majority of males were circumcised (>60%) and most of the patients were Lebanese (>80 %) (Table 1).

E. coli was the most common pathogen isolated among both groups, followed by Klebsiella and Proteus species (P-value<0.0001) (table 1). Other organisms such as Pseudomonas, Enterococcus, and Enterobacter were relatively rare. The proportions of ESBL-producing organisms causing UTI were 25.7% in 2012, 26% in 2013, 42.9% in 2014, 36.2% in 2015, 46.4% in 2016 and 48.3% in 2017 (Figure 1).

Renal and bladder ultrasound has been done in all patients except 35 (79.1 %) (Table2) since imaging could be done in outside basis and results were not available. Normal ultrasound was dominant in both groups with 72.5% and 68.5% in ESBL and non ESBL respectively and non significant (P-value= 0.52). Positive findings ranging between renal fullness, pelvicalyceal dilatation and prominent papillae were seen in 27.5% of ESBL and 31.5% in non ESBL groups.

Results of VCUG were available only in 20.6% of all patients, since this screening was not always available in our hospital and results of imaging done outside could not be reached. Of those 58 results normal findings were similar in both groups (71.4% and 73.3% in ESBL and non ESBL groups respectively with P-value= 0.87) (Table 2). Positive findings with different stages of vesicourethral reflux were also similar in both groups (28.6% and 26.7% respectively); however, we noticed advanced stages of VUR grade 3 and 4 in ESBL group to be more common.

DMSA screening is not available in our hospital, but of 7 results that were done in other institution, only one result was normal and the other 6 findings ranged between scars and decrease renal function were related to advanced stage VUR and ESBL group. Urine analysis showing positive results including WBC of more than 5 in HPF with positive leukocyte esterase and nitrite were similar in both groups.

When comparing clinical presentation and laboratory findings, there was a significant difference in presenting fever which is most common in non ESBL group (72.4% compared to 56.3% in ESBL group, P-value= 0.007), in contrast to dysuria which was more common in ESBL group (35.9% vs. 21.9%, P-value= 0.012). Mean length of hospital stay was significantly higher in ESBL group (8.82 vs 5.50 days, P-value<0.0001). Hemoglobin and neutrophil count were significantly higher in non ESBL group. On the other hand, there was no significant difference in other symptoms like febrile days duration prior to presentation, frequency and abdominal pain. Also there was no significant difference in other laboratory findings such as WBC, platelets count CRP level, urine analysis findings and radiologic ultrasound results (Table 3).

Although renal disease, genitourinary surgery, immunocompromised and failure to thrive were more

prevalent in ESBL cases, the difference was not statistically significant. On the other hand, vesicourinary reflux, recurrent UTI, non GU surgery, previous antibiotic use and recent hospitalization within one month were found to be significantly higher in the ESBL group (Table 4).

There is a strong resistance to beta lactam antibiotics while the highest is for ampicillin and amoxicillin, followed by the 3rd generation cephalosporins. On the contrary, there was a complete sensitivity to carbapenems. Bactrim had 50% resistance in the pathogens (Table 5). The choice of antibiotics was related to the isolated pathogen recovered in culture. 3rd generation cephalosporins (cefotaxime,ceftriaxone) are the most common used when sensitive pathogen was isolated. In contrast to ESBL group the carbapenems were the first choice (Table 6).

DISCUSSION

Urinary tract infection is a common infectious disease in the pediatric age group. The epidemiology of pediatric UTIs depends on several factors such as age, gender, and genitourinary malformations. Our study showed an overall female predominance; this could be related to circumcision as 60 % of males in our study were circumcised. This is presumed to be the result of geographic location and religious affiliation.[15] In addition, the shorter female urethra is a plausible explanation of the increased prevalence of UTIs in females. Zorc et al. mentioned that UTI is prevalent in all children in their first year but after 1 year of age, it tends to decrease in males due to multiple factors such as circumcision.[15] 70 % of infected patients had a normal ultrasound. This could be explained by that ultrasound imaging is an operator dependent and the range of mistakes could be wide.

The present study revealed that E. coli is the most common pathogen in UTIs among all age groups, whether ESBL or non-ESBL producers. This finding is compatible with other studies.[1,2,11,16] There were no statistically significant differences in the presenting symptoms between ESBL and non- ESBL UTI, although our study showed that high grade fever, irritability and vomiting are more common in non ESBL group in contrast to a study done by Dotis et al[16] that showed children with ESBL UTI presented clinically with more symptoms than children with non-ESBL UTI.

Some of the risk factors for ESBL UTI that our study showed to be significant were recurrent UTIs, previous urological abnormalities, previous antibiotic use, and previous hospitalization. These were found to be significant in other studies.[1,2,11,12,13]

AAP recommends to do renal and bladder ultrasound in each febrile UTI patient; however, VCUG is indicated if RBUS reveals hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances. Also it should be conducted if there is a recurrence of febrile UTI.[9,10] As for patients who had vesicourethral reflux we documented a high rate of ESBL infection although the P value is in the upper limit (0.08) and this can be explained that patients who had VUR develop more episodes of UTI and they are more exposed to different types of antibiotics. Strysko et al showed also that international travel and Asian race were found to be a significant risk factor for ESBL acquisition.[5]

The mean length of hospital stay was significantly longer for patients with UTI caused by ESBL-producing bacteria than that for patients with UTI caused by non-ESBL-producing bacteria. This may be attributed to the fact that ESBL treatment in children necessitates parenteral antibiotic administration for 7–10 days; as opposed to adults, where oral Ciprofloxacin is a treatment option for ESBL UTI. Other studies also found that longer hospitalization periods are needed for the treatment of ESBL infections (Lautenbach et al., 2001; Megged, 2014).[12,13]

Over the 6-year period that the present study was conducted, there was an alarming increase in the incidence of ESBL-producing UTIs in hospitalized children, from 25.7% in 2012 to 48.3% in 2017. However, we noticed a small decrease in the number admitted in 2015. A Lebanese study done by Araj et al showed an increase of ESBL-producing E. coli and Klebsiella spp, from 4 and 12% in 2000 to 30% and 28% in 2011, respectively.[14] A comparable finding was also demonstrated at another center in Lebanon by Daoud et al., who observed an increase in UTIs caused by ESBL-producing organisms from 2.3% in 2000 to 16.8% in 2009 among patients of all ages.[6] Both studies attributed this finding to uncontrolled antimicrobial usage in Lebanon (Daoud and Afif, 2011; Araj et al.,2012). Hanna –Wakim et al showed also an increase from 8% in 2001 to 25% in 2011.[1,6,14]

We observed in our study a significant resistance to cephalosporins especially 2nd and 3rd groups, and approximately total resistance to monobactams. This could be explained by the prescription abuse of these types of antibiotics and the absence of stewardship programs that limit the overuse of antibiotics in the community. In contrast we noticed a full sensitivity to carbapenems and this was probably because these types of antibiotics are available only in intravenous injection and are hospital dependent. Our study showed that Bactrim has 50% resistance in the pathogens isolated which make it appropriate oral antibiotic when sensitivity is available.

Although this study in one of limited studies that looked for hospitalized cases of UTI and the associated risk factors for ESBL acquiring, there are certain limitations that should be noted. Our study only examined

hospitalized children with UTI, and therefore our findings may not apply to the general pediatric population. Furthermore, the number of cases included in our study was restricted by our criteria for defining UTI. A significant number of cases excluded due to negative or low colony count on urine culture are likely the result of over-the-counter antibiotic use before the culture was taken. Another limitation is the capacity of the hospital since VCUG and DMSA images are not available. Finally, our study is not immune to the inherent limitations of a retrospective chart review; the cases included in our study were limited by the availability of data and incomplete medical records, such as missing laboratory results for urine cultures or other studies that were done in outside hospitals.

In conclusion, the resistance to commonly used antibiotics for UTIs has been increasing over the last 6 years, as ESBL producing organisms are emerging. The recognition of the epidemiology and risk factors for ESBL-producing bacteria in the pediatric population may affect our management and therapeutic approach. In keeping with our finding that previous antibiotic use was the most important independent risk factor for emergence of ESBL-producing bacteria, further studies and new recommendations that guide management of UTIs and antibiotic use are warranted. Oral antibiotics such as Bactrim could be an alternative oral treatment when sensitivity is available.

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