



ESBL PRODUCING ORGANISMS PROFILE FROM URINARY TRACT ISOLATES IN CHILDREN, A SINGLE CENTER STUDY

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ABSTRACT

Background: Urinary tract infection (UTI) remains one of the most common infections diagnosed in outpatients and in hospitalized patients. Current knowledge on antimicrobial susceptibility pattern of uropathogens is mandatory for appropriate therapy. Extended spectrum Beta-lactamase (ESBL) producing bacteria; as a part of multidrug resistant (MDR) Gram-negative bacteria, are growing problems. ESBL hydrolyzes expanded spectrum antibiotics like Cephalosporins which are used in the treatment of UTI. **Objectives:** The primary aim of this study is to define the profile of acquisition of extended spectrum beta-lactamase (ESBL) producing bacteria in children seen in King Talal Military Hospital with community acquired urinary tract infections and to evaluate their antimicrobial resistance. **Methods:** This retrospective study was conducted by reviewing medical records in the microbiology laboratory in King Talal Military Hospital which serves the Eastern area of Jordan, Almafraq Governorate. Urine culture results in pediatric patients in two years period between January 2023 to December 2024, in which antimicrobial sensitivity of urinary isolates also was identified, were included and all samples were screened for ESBL production. **Results:** A total of 1058 patients in our study grew Gram-negative bacteria urinary isolates over the study period. 196 cases were with ESBL-producing strains and 862 cases with non-ESBL producing Gram negative bacteria. Most of the ESBL-producing organisms isolated were sensitive to carbapenems (100% of ESBL organisms susceptible to ertapenem and 96.9% susceptible to imipenem and meropenem) and Amikacin (95.9 % of ESBL organisms susceptible). **Conclusion:** ESBL producing organisms are emerging problem that accounts for a significant percentage of organisms that were isolated from urine cultures in pediatric patients in Almafraq.

KEYWORDS: urinary tract infection, extended spectrum beta-lactamase, antimicrobial resistance.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common pediatric infections worldwide.^[1] It may cause permanent kidney injury,^[2] whereby early diagnosis and treatment is needed to prevent scarring. Urinary tract infections are more common in females than males.^[3]

The symptoms and clinical picture of UTI vary according to patient's age.^[4] No one specific sign or symptom can be used to identify UTI in infants and young children. Children older than 6 years and adolescent can display specific symptoms suggestive of UTI.^[5]

The criteria for the diagnosis of UTI in children are the presence of pyuria and /or bacteruria on urinalysis and of at least 50,000 colony forming units (CFU) per ml of a uropathogen from the quantitative culture of a properly collected urine specimen.^[6]

There are two broad clinical categories of UTI are pyelonephritis (upper UTI) and cystitis (lower UTI). The most common causative organisms are bowel flora, typically Gram-negative rods.^[7] Escherichia coli (E. coli) is the most common organism isolated from pediatric patients with UTI, (more than 90 % of all uncomplicated UTIs are caused by E.coli),^[8] followed by Klebsiella

species. However, other organisms that may gain access to the urinary tract can cause infection, including Fungi (*Candida* species) and viruses.^[9]

Because *Escherichia coli* and *Klebsiella* species are the most pathogens, empirical treatment by choosing a third generation cephalosporin in acute pyelonephritis is preferable. However, *Escherichia coli* and *Klebsiella* have variable antimicrobial resistance mechanisms which may include the production of extended spectrum beta-lactamase (ESBL). Extended spectrum beta-lactamases (ESBLs) are enzymes produced by a variety of Gram negative bacteria which hydrolyze commonly used antibiotics and confer an increased resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam,^[10] but no effect on cephalosporins, carbapenems and related compounds.^[11]

Unfortunately, the excessive application of antibiotics in different health centers and the common overuse and misuse as well as neglected local community susceptibility profiles, resulted in the emergence of antimicrobial resistance in uropathogenic bacteria across the globe,^[12,13] ESBL producing Gram-negatives (drug resistant pathogens) are a major concern and worrying global public health issue as infections caused by such enzymes – producing organisms are associated with a higher morbidity and mortality, longer hospitalization periods and greater financial burden.^[14]

Antibiotics are usually given empirically before the laboratory results of urine culture are available. To ensure appropriate therapy, current knowledge of the organisms that cause UTI and their antibiotics susceptibility is mandatory.^[15]

The purpose of this study is to obtain data about the susceptibility patterns of pathogens responsible for urinary tract infections (UTIs) in pediatrics in Almafra to the currently used antimicrobial agents.

METHODS

This retrospective study conducted in King Talal military Hospital. The records of pediatric patients who were hospitalized or seen in outpatient clinics with a diagnosis of UTI with positive urine culture between 1 January 2023 and 31 December 2024 were reviewed. The study included children from 0-14 years.

A total of 5689 urine cultures were requested in our hospital during 24-month study period. The specimens were inoculated onto blood and MacConkey agar. All plates were incubated at 37°C for 24 hours. Urinary isolates were identified by conventional methods. Only one isolate per patient was included in the study. All isolates were tested for antimicrobial susceptibility by disc diffusion method. Those with no growth or mixed growth of organisms were excluded.

ESBLs production in our study was determined by double disc synergy test technique using antibiotics discs containing cefotaxim, ceftazidime, cefepime either alone or in combination with clavulanic acid. Susceptibility testing to other antibiotics was performed by disc diffusion method. The following antibiotic discs were used: ampicillin, amikacin, cefotaxim, amoxicillin/clavulanic acid, piperacillin/tazobactam, ceftazidime, cefepime, ertapenem, imipenem, meropenem, gentamicin, nalidixic acid, nitrofurantoin, and trimethoprim/sulfamethoxazole.

RESULTS

During the period of the study, a total of 1058 patients had one or more urine cultures grow Gram-negative bacteria. Out of these, 430 were associated with significant pyuria and/or bacteruria. Our study excluded cultures with gram positive bacterial growth, which was seen in 102 isolates. Out of the 1058 patients with gram negative bacterial growth, 970 patients were females (91.6%) and 88 cases (8.3%) were males (with a ratio of 11:1). The isolates collected from these patients included *Escherichia coli* from 852 patients (80.5%), *Klebsiella* species from 126 patients (11.9%), *Enterobacter* species from 34 patients (3.2%), *Pseudomonas* species from 28 cases (2.6%) and 18 cases with proteus species (1.7%). Out of these cases, 196 cases grew an ESBL-producing Gram-negative organism (18.5% of the all Gram-negative isolates). 164 cases of the ESBL-producers were *E. coli* (83.6%), 30 cases grew *Klebsiella pneumoniae* (15.3%) and only two cases had *Enterobacter cloacae* (about 1%). See table 2. With a higher female to male ratio for ESBL isolates (15:1), 184 females patients and 12 males, see table 1.

Most ESBL organisms were susceptible to the tested carbapenem antibiotics, 100% susceptibility to ertapenem with only 6 cases having intermediate resistance to meropenem and imipenem with sensitivity 96.9%. Most isolates were susceptible to Amikacin (95.9%) with only 8 isolates, 2 *Klebsiella pneumoniae* and 6 *E. coli* isolates, having intermediate resistance. Fewer than two thirds of the ESBL producing organisms tested were susceptible Piperacillin/Tazobactam (60%) and Nitrofurantoin (61.8%), but more three quarters were susceptible to gentamicin (78.1%). Susceptibility to trimethoprim/sulfamethoxazole and nalidixic acid was low at 30.9% and 27.2%, respectively. Of the 196 bacterial pathogens studied, antibiogram revealed that 196 (100%) and 178 (91%) isolates are resistant to ampicillin and ceftazidime, respectively indicating maximum resistance to these drugs. See table 3.

Table 1: Demographics.

Gender	ESBL isolates Number (%)	Non-ESBL isolates Number (%)	All gram negative isolates Number (%)
Males	12 (6.1%)	76 (8.8%)	88 (8.3%)
Females	184 (93.8%)	386 (91.2%)	970(91.6%)
Total	196	862	1058 (100%)

Table 2: Etiologic agents for UTI.

Causative agents	ESBL producing (number of isolates)	Non-ESBL producing (number of isolates)	Total gram negatives
E. coli	164	688	852 (80.5%)
Klebsiella species	30	96	126 (11.9%)
Enterobacter sp.*	2	32	34 (3.2 %)
Pseudomonas sp.	—	28	28 (2.6%)
Proteus sp.	—	18	18 (1.7 %)
Total	196 (18.5 %)	862 (81.5%)	1058 (100%)

*species.

Table 3: Antibiogram of isolated ESBL-producing E.coli and K.pneumonia.

Klebsiella pneumonia (%)	Escherichia coli (%)	Antibiotic
0%	0%	Ampicilin
87.5%	95.9%	Amikacin
25%	12.7%	Cefotaxime
25%	10.9%	Ceftazidime
25%	9%	Cefepime
100%	100%	Ertapenem
87.5%	96.9%	Imipenem
87.5%	96.9%	Meropenem
75%	78.1%	Gentamicin
12.5%	25.4%	Amoxicillin/Clavulanic acid
74%	61.8%	Nitrofurantoin
50%	30.9%	Trimethoprim / sulfamethoxazole
62.5%	27.2%	Nalidixic acid
25%	60%	Piperacillin Tazobactam

The table above shows how ESBL-producing E.coli and ESBL-producing klebsiellae pneumonia differ in their antibiotic susceptibility. Both groups have same level of sensitivity to ertapenem. However, klebsiellae pneumonia showed higher levels of resistance for imipenem and meropenem, while having better susceptibility to Trimethoprim / sulfamethoxazole and Nalidixic acid.

DISCUSSION

Various organisms have been reported to be isolated from patients with UTI. E.coli^[16] and Klebsiella^[17] have been reported as the most common organisms causing UTI. Of all pediatric patients with urine cultures positive for Gram-negative organisms at our hospital from January 2023 and December 2024, 18.5 % grew an ESBL organisms. These ESBL-producing organisms demonstrated the least resistance to carbapenems and amikacin, based on susceptibility results.

ESBLs are now a problem throughout the world. The prevalence of ESBLs among clinical isolates vary greatly worldwide and in geographic areas and are rapidly changing over time.^[18] The occurrence of ESBL

producers in urinary isolates of E. coli and K. pneumoniae in our study was found to be 19.2 and 23.8% respectively. This is higher than he reported figures of E. coli and K. pneumoniae in USA (2.2 /6.6%), Canada^[19] (2.7/6.2%). Much higher (58%) prevalence of ESBL producers in urinary isolates of gram-negative bacilli was observed in India by Mathur et al.^[20] In comparison to our study, 2004 report from Poland described 11.5% of urine isolates as ESBL producers in children.^[21] We had a higher percentage of ESBL-producing klebsiella pneumoniae (23.8%) but a similar percentage of E.coli (19.2%) ESBL producers. Of note, ESBL-producing P mirabilis was found in 10% of their isolates; however our institution did not test for ESBL-producing P mirabilis.

False susceptibility observed in our study to third generation cephalosporins in due inoculum effect.^[22] ESBL production coexisted with resistance to several other antibiotics. ESBLs are encoded by plasmids, which also carry resistant genes for other antibiotics.^[23] We found such associated resistance with co-trimoxazole 70% and fluoroquinolones – 96%. Since co-resistance to non-beta lactam antibiotics like co-trimoxazole and

nalidixic acid was observed, amikacin and nitrofurantoin are found to be alternatives for treatment at low cost.

Limitations of this study include reliance on retrospective data. Also, the patients in this study had urine cultures positive for Gram-negative organisms, but they did not necessarily have true urinary tract infections; however, it is important to be aware of risk factors for colonization of resistant bacteria as well, since colonization with ESBL-producing *K. pneumoniae* has been suggested to lead to infection in the neonatal ICU.^[24]

CONCLUSION

ESBL-producing strains are a growing problem that necessitate a proper evaluation for antibiotics susceptibility to better management of urinary tract infections. ESBL production has been observed in a large percentage of urinary isolates. UTI due to ESBL-producing organisms are emerging. Patients infected with these strains cannot be treated with beta-lactam antibiotics and monobactams. Because of increasing antibiotic resistant rates of *E. coli* to a number of commonly used antibiotics to an alarming level, guidelines for the management of UTIs must be revised. Nitrofurantoin is recommended for the first-line empirical oral treatment of uncomplicated UTIs.

Appropriate estimates of ESBL infections when coupled with other mechanisms of resistance will allow for appropriate targeting of resources toward research, drug discovery, antimicrobial stewardship, and infection control.

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