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# Extended-Spectrum beta-lactamase ---Producing Enterobacteriaceae Causing Urinary Tract Infections in Children in Qatar



Mahmoud Alhandi Omar Helal MD<sup>1,2\*</sup>, Khalid Al Ansari MD<sup>3,4</sup> Colin Powell MD<sup>3,5</sup>

<sup>1</sup>Division of Pediatric Emergency Medicine, Department of Pediatrics, Hamad Medical Corporation, Qatar

<sup>2</sup>Pediatric Nephrology Department, Aleppo University, Faculty of Medicine, Aleppo, Syria

<sup>3</sup>Emergency Department, Sidra Medicine, Doha, Qatar

<sup>4</sup>Weill Cornell Medical College, Cornell University, Doha, Qatar

<sup>5</sup>School of Medicine, Cardiff University, Cardiff, UK

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**\*Corresponding author:** Dr. Mahmoud Alhandi Omar Helal, MD: Paediatric Department, Hamad Medical Corporation, PO Box 3050. Doha, Qatar.

ORCID ID: Mahmoud Alhandi Omar Helal <https://orcid.org/0000-0002-4026-3169>

## Abstract

**Objectives:** Urinary tract infections (UTI) in children are most frequently due to Enterobacteriaceae. Multidrug-resistant *Escherichia coli* including extended-spectrum beta-lactamase (ESBL) producing organisms are becoming more prevalent. The aim of this study was to describe a cohort of children with ESBL producing organism urinary tract infections and the organism susceptibility patterns.

**Methods:** This retrospective study evaluated a cohort of children with ESBL- induced UTI, admitted to our Pediatric Emergency Centre during a 2.5-years period.

**Results:** In a total of 633 patients with urinary tract infection, 115 (18.2%) grew Gram-negative urinary isolates with an ESBL strain. Among of them (80%) female, (25.2%) had urinary tract abnormalities and (4.3%) had neuromuscular disorders. The most common bacteria were *E coli* (77.4%) then *Klebsiella pneumonia* (14.8%). All of the ESBL organisms were sensitive to carbapenems, with 98.7% sensitive to Amikacin, and 83% sensitive to Gentamicin. Gentamicin was used in (56.5%), Amikacin (23.5%) and Ertapenem/Meropenem (20.0%) of cases. The duration of treatment was 5-7 days but two cases relapsed.

**Conclusion:** The proportion of urinary tract infection induced by ESBL organisms was almost 1 in 5 of patients. Carbapenems and aminoglycoside remained the corner stone in treatment of the urinary tract infection by ESBL produced organisms with very high efficacy, most cases responded to treatment within 5-7 days of intravenous single antibiotic.

**Keywords:** Extended spectrum beta -lactamase; Urinary Tract Infection in children; Aminoglycoside

**Abbreviations:** UTI: Urinary Tract Infections; ESBL: Extended spectrum beta -lactamase

## Introduction

Urinary tract infections (UTIs) are the most common bacterial infections in paediatric practice. The emergence of multi resistant extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae (ESBL) as a cause of UTI is a major concern because therapeutic options are limited.

The World Health Organization and the European Commission have recognized the importance of studying the emergence and determinants of acquired anti-microbial resistance and the need to initiate appropriate strategies for their control [1]. In particular, the ESBL-producing *Escherichia coli* are emerging worldwide. The ESBL-producing strains are becoming resistant to most of the oral

and intravenous antibiotics. Furthermore, they are often cross-resistant to trimethoprim/sulfamethoxazole and quinolones. This combination of properties can significantly affect the course and outcomes of infections, both in the community and in the hospital setting. International guidelines emphasize oral antibiotics as first-line treatment of UTIs in children [2]. There are no oral antibiotics for first-line treatment is active against ESBL and there are few intravenous antibiotics options. Carbapenems remain the standard treatment for severe infections due to ESBL [3], but uncontrolled use of carbapenems has led to the emergence of carbapenem as producing Enterobacteriaceae which are resistant to many antibiotics.

Reserving carbapenems when alternative treatment exists is a therapeutic challenge. Recent French guidelines recommend amikacin as a first-line treatment after reviewing the increase in prevalence of ESBL strains and the need to spare the carbapenems. In this study, we describe the patients with an ESBL-producing urinary tract infection in children hospitalized from a paediatric emergency department and characterize the antibiotic susceptibility patterns of these organisms and compare the antibiotic choices along with duration of treatment.

### Materials and Methods

**Study design:** A retrospective cohort study

**Study setting:** Pediatric Emergency Department (PED) at Hamad General Hospital in Qatar state, which is the main PED in Qatar state which has 4 stations all over Doha city connected to each other by electronic systems (Cerner TM) for documentations, with annual patients visiting of average 335,000 and also providing primary care.

**Study duration:** January 2015 to August 2017

**Patient identification:** All patients who had a microbiological diagnosis of UTI, using the electronic medical records (Cerner), over that time period.

**Microbiological methods:** The method for assessment of ESBL production is Phoenix instrument with E-test for confirmation. The Phoenix has a built-in algorithm that flags isolates as potential ESBL producers, and this is confirmed phenotypically by using E-test strips that contain ceftazidime and cefotaxime with and without clavulanic acid. Antibiotic susceptibility testing was conducted by using the Clinical and Laboratory Standards Institute cut off method. Antibiotic susceptibilities of the ESBL organisms obtained were assessed.

### Clinical demographics

Patient characteristics evaluated for ESBL risk were extracted from the institution's electronic patient records.

**Table 1:** Characteristics of a cohort with ESBL urinary tract infection.

Characteristics	n=115
Age, years, mean (SD)	2.07 (2.91)
Gender Male (%)	23 (20)
<b>Other associated conditions n (%)</b>	
Urinary tract abnormalities*	29 (25.2)
Neuromuscular disorder **	5 (4.3)
<b>Organisms n (%)</b>	
<i>Escherichia Coli</i> (ESBL)	89 (77.4)
<i>Klebsiella pneumoniae</i> (ESBL)	17(14.8)
<i>Citrobacter freundii</i> (ESBL)	3(2.6)
<i>Morganella Morgagni</i> (ESBL)	2(1.7)
<i>Enterobacter cloacae</i>	3(2.6)
<i>Proteus Mirabilis</i>	1(0.8)

- a) Pediatric patients who presented with symptoms and signs suggested of urinary tract infections or
- b) Nonspecific complaints and were diagnosed as UTI with urine cultures growing Gram-negative bacteria

### Results

There were 633 patients who visited our PED with symptoms suggestive of UTI who had positive urine cultures. 115 out of total 633 (18%) urine samples found to be ESBL. They were admitted to hospital for treatment with intravenous (IV) antibiotics. None of these 115 patients were sick and all of them received the first dose of the antibiotic in the hospital then completed the IV course of antibiotics in the antibiotic clinic as outpatients.

During the period from 2015 to 2017, over 800,000 paediatric patients visited the PED. A total of 633 patients identified to have urinary tract infection, urinary tract infection (UTI) is defined as positive leucocyte esterase or nitrite by urine dipstick or >5 WBCs/hpf or  $\geq 5 \times 10^4$  colonies/mL in a catheterized urine specimen or, in older children, by clean catch specimens with  $\geq 10^5$  colonies/mL. All urine cultures (633) grew Gram-negative organisms. The proportion of patients with ESBL-producing isolates was 115 (18%) cases out of total number of patients with UTI (633).

Most of the ESBL organisms isolated were sensitive to carbapenems (100%), Amikacin (98.7%). Gentamicin was used in (56.5%), amikacin (23.5%) and ertapenem/ meropenem (20%). Two cases had 2nd UTI with the same initial bacteria (*E-coli* and *K. Pneumoniae*) within one month from treatment and were treated successfully. Fever was identified in 23 cases (26.45%) on presentation, abdominal pain in 21 cases (24.15%), urinary symptoms in 77 cases (67.3%), and poor feeding with irritability especially between infants 8 cases (6.9%). There were (25.21%) of patients known to have urinary tract abnormalities and (4.34%) had neuromuscular disorders. (Table 1: Characteristics of a cohort with ESBL urinary tract infection).

Medications n (%)	
Gentamicin	65 (56.5)
Amikacin	27 (23.5)
Ertapenem/ Meropenem	13 (11.3) / 10 (8.7)
Repeated first negative c/s	
Median (Minimum – maximum)	3 (2 – 11)
2days	21 (18.3)
3days	10 (8.7)
4days	5 (4.3)
5days	4 (3.4)
6 days	3 (2.6)
8 days	1 (0.9)
Not repeated	71 (61.7)
Duration of antibiotics (%)	
Median	6
3day	18 (15.7)
4 day	17 (14.8)
5 day	16 (13.9)
6 day	41 (35.7)
7 day	14 (12.2)
8 day	7 (6.0)
9 day	2 (1.7)

\*Urinary Abnormalities-Ureterocele, left side hydro nephrosis, Vesico-ureteric reflux, bilateral hydro nephrosis with VUR, ectopic kidney, unilateral mild nephron calcinosis, multi cystic kidney

\*\*Neuro muscular-spina bifida with cyst, Microcephaly

## Discussion

Our study suggests that amikacin could be the drug of choice for UTIs due to ESBL in children. Furthermore, amikacin can be administrated as a daily single dose. Moreover, pharmacokinetics and pharmacodynamics of aminoglycosides, in particular their reduced bile and digestive elimination suggest a lower impact on intestinal flora [4]. Carbapenems are considered the most reliable treatment for infections caused by ESBL-producing bacteria as we mentioned above [5]. Despite their utility, resistance has emerged, which has led to finding alternative antibiotics for UTIs. Han *et al.* recently described their positive retrospective experience with aminoglycosides in UTIs due to ESBL-E [6]. The daily administration of an aminoglycoside with 30-min IV infusion for average 5 days has been shown to promote tissue diffusion and renal concentration while limiting renal and hearing toxicity [7]. Nitrofurantoin and fosfomycin are commonly used to treat cystitis in adults [8] but there are no data on their efficiency in UTI by ESBL in children. The tolerance of nitrofurantoin needs to be investigated further in children [5].

In our cohort, the susceptibility pattern of isolated ESBL was similar to that found in hospitals from Northwest England and North Wales between 2007 and 2012 [9]. In the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Canada and the United States, susceptibility to amikacin remained high, between 95.4% and 100% [10]. This variability in antimicrobial

susceptibility patterns among ESBLs between studies depends on local epidemiology according to the levels and types of plasmid-mediated resistance genes.

One limitation of the study is that 60% of patients did not have their urine cultured after finished the antibiotic course. These patients were followed up by telephone and by tracked electronically for an unexpected PED visit for urine related complaints over the 2 weeks following the initial infection. Only 2 children had prolonged urinary symptoms but none had side effects.

## Conclusion

The emergence of extended-spectrum  $\beta$ -lactamase – producing Enterobacteriaceae (ESBL) as a cause of UTI presents could become a serious problem. We believe that amikacin should increasingly play a key role in the therapy of UTI due to ESBL in children, hence avoiding the use of carbapenems. Most cases can be treated for 5-7 days effectively and without any side effects.

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## Authors' contributions

MAOH. And KA. Designed the study; MAOH. And CP. collected

data; MAOH. And CP. analysed the data; MAOH, KA. And CP. wrote the main manuscript. All authors reviewed and agreed to the published version of the manuscript.

## Availability of Data and Materials

All data generated or analysed during this study are included in this article. Further inquiries can be directed to the corresponding author.

## Declarations

### Ethics approval and consent to participate:

This study was approved by the Institutional Review Board (IRB) of the Medical Research Center at Hamad Medical Corporation.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no conflict of interest.

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