Frequency of infections caused by ESBL-producing bacteria in a pediatric ward – single-center five-year observation

Agata Będzichowska¹, Jędrzej Przekora¹, Angelika Stapińska-Syniec², Aneta Guzêk³, Piotr Murawski⁴, Katarzyna Jobs¹, Barbara Wróblewska⁵, Bolesław Kalicki¹

¹Department of Pediatrics, Pediatric Nephrology and Allergology, Military Institute of Medicine, Warsaw, Poland
²Students' Academic Club at the Department of Pediatrics, Pediatric Nephrology and Allergology, Military Institute of Medicine, Warsaw, Poland
³Department of Medical Diagnostics, Military Institute of Medicine, Warsaw, Poland
⁴Information and Communication Technology Department, Military Institute of Medicine, Warsaw, Poland
⁵Department of Immunology and Food Microbiology, Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences, Olsztyn, Poland

Submitted: 2 January 2017
Accepted: 9 March 2017

Arch Med Sci
DOI: https://doi.org/10.5114/aoms.2017.72407
Copyright © 2019 Termedia & Banach

A b s t r a c t

Introduction: Infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) are a serious therapeutic and clinical problem. An increasing role of ESBL(+) pathogens is observed in both community- and hospital-acquired infections.

Aim of the study was to assess the incidence and the risk factors for ESBL(+) bacteria infection in a pediatric ward during a 5-year period.

Material and methods: The medical documentation data of patients hospitalized in the Department of Pediatrics, Pediatric Nephrology and Allergology between 2011 and 2015 were subjected to a retrospective analysis. Cases of ESBL(+) bacterial infections were analyzed in detail.

Results: 0.57% (46) of all the hospitalizations (8015) during the 5-year observation period in our department were caused by ESBL (+) pathogens. It constituted 8.5% of all positive microbiological cultures obtained. The analysis revealed an increasing trend in the number of ESBL (+) infections throughout the observed period. 43.5% of patients were only asymptomatic carriers. In 71.7% urinary tract structural and functional abnormalities were present. 76.1% of patients had been hospitalized previously and 60.9% had undergone urinary tract invasive procedures.

Conclusions: The results confirm the rising trend of ESBL (+) infections during the observed period. ESBL (+) bacteria were isolated primarily in previously hospitalized children with particular reference to urinary tract invasive procedures during hospitalizations. Moreover, the study showed that patients with urogenital disorders and non-urinary chronic diseases are more susceptible to these priority pathogen infections.

Key words: extended-spectrum β-lactamases, multidrug resistance, risk factors, children, urinary tract infections.

Introduction

Priority pathogens are biological infectious agents characterized by particular virulence and drug resistance. One of the most important fam-
ilies of priority pathogens is Enterobacteriaceae spp. such as Klebsiella pneumoniae and Escherichia coli producing extended-spectrum β-lactamases (ESBL (+)) [1, 2]. The incidence of infections caused by ESBL (+) pathogens is increasing every year, mainly because of inadequate antimicrobial therapy [3–6]. ESBL (+) pathogens are becoming a major challenge in clinical practice, causing hospital-acquired infections in patients who have undergone multiple hospitalizations as well as community-acquired infections in outpatients [3, 4, 7–13].

Extended-spectrum β-lactamases is a rapidly evolving group of enzymes capable of decomposing the majority of β-lactam antibiotics such as third-generation cephalosporins and aztreonam, but not active towards cephemycins, carbapenems and β-lactamase inhibitors [5, 6, 11, 12]. Penicillins with β-lactamase inhibitors reach high concentrations in urine and can be used in treatment of urinary tract infections (UTIs) caused by ESBL (+) pathogens [8]. Carbapenems still remain the gold standard of treatment for serious pediatric ESBL (+) infections [1, 12, 14]. Ertapenem and imipenem are considered to be the most effective antibiotics against ESBL (+) E. coli strains [15], but in some cases after antibiogram results the therapy can be changed to non-carbapenem alternatives such as fluoroquinolones, aminoglycosides, nitrofurans, co-trimoxazole [1, 4, 8, 14].

Due to plasmid location of ESBL genes there is a risk of gene transfer to another resistant strain and development of plasmid-mediated multidrug resistance, which limits the therapeutic possibilities [1, 12, 14].

Extended-spectrum β-lactamases (+) strain infections are becoming a growing problem in empirical treatment for doctors around the world. In our study we want to show the demographics, risk factors and treatment outcomes of pediatric patients infected by ESBL (+) pathogens from 5-year experience in our clinic.

Material and methods

The medical documentation data of patients hospitalized in the Department of Pediatrics, Pediatric Nephrology and Allergology, Military Institute of Medicine, Warsaw, Poland between January 2011 and December 2015 were included in the retrospective analysis.

Records of ESBL (+) bacterial infections were separated among documentation of all hospitalized children and subjected to a detailed analysis. Age, gender, severity of infection, urinalysis, antibiotic selection according to the antibiogram and outcome were considered. A correlation between the presence of ESBL (+) bacteria in the analyzed sample and clinical status and indicators of inflammation was also included. The children fulfilling the criteria for symptomatic infections and asymptomatic carriers were separated.

Identification of isolates was performed by an automated system for identification, VITEK2. All the strains were classified as ESBL(+) by the method of double discs.

Statistical analysis

The results are presented as the mean value and percentages. The obtained data were analyzed by means of Microsoft Excel and analytics software Statistica. The resemblance of a particular variable distribution to the normal distribution was tested by Shapiro-Wilk and Wilkinson tests.

Results

Among 8015 hospitalizations and 537 positive cultures of biological material performed in the 5-year-period, 46 ESBL (+) infections were recorded, which constituted 0.57% of all hospitalizations and 8.5% of all positive microbiological tests. The analysis revealed an increasing trend in the number of ESBL (+) infections between January 2011 and December 2015 (Figure 1).

The mean age of analyzed children was 5.35 years and 65.2% of patients were female. 43.5% of patients were asymptomatic carriers. 76.1% of patients had a history of previous hospitalization and in 17 (37%) cases there was more than one hospitalization. The mean time from the last to current hospitalization was 2.3 months. 71.7% of patients had urinary tract structural or functional abnormalities such as urolithiasis, horseshoe kidney, dilation of the renal pelvis and calyces, recurrent urinary tract infections, vesicoureteral reflux, hypercalciuria, nephrotic syndrome, urosepsis in anamnesis and neurogenic bladder. 60.9% of the patients had a history of urinary tract related procedures such as URSL, ESWL, urography, cystoscopy, cystography, laparotomy, retrograde intrarenal surgery and urodynamic testing. The mean time

![Figure 1. Number of ESBL (+) infections during the years 2011–2015](image-url)
Frequency of infections caused by ESBL-producing bacteria in a pediatric ward – single-center five-year observation

between the last procedure and ESBL (+) urine culture was 7 months; however, if we rule out one diacritical case (8 years from the last procedure) the mean time changes to 3.3 months. 28.26% suffered from chronic illness other than urinary system diseases and anomalies, especially neurological pathologies such as myelomeningocele, epilepsy, cerebral palsy, paresis, mitochondrial encephalopathy, as well as asthma and allergy. Death has not been reported as a result of ESBL (+) infections. All patients were treated with good results and discharged from the clinic in good clinical condition. Results are summarized in Table I.

Due to the nephrological character of the department ESBL (+) pathogens were mostly identified from urine cultures and only in 1 case from wound swab culture. The two most common pathogens were E. coli ESBL (+) and K. pneumoniae ESBL (+). Only in one case did the results of microbiological tests reveal the presence of two causative priority pathogens (Table II).

Depending on laboratory results and clinical state the empirical antibiotic monotherapy was cefuroxime in 19.6%, amikacin in 8.7% and amoxicillin with clavulanic acid in 6.5% out of 46 cases. In 9 (19.6%) cases more than one drug was used in the therapy (Table III). After obtaining the results from bacterial culture the therapy was modified according to antibiogram results. In all cases ESBL (+) bacteria were susceptible to carbapenems. The resistance to fluoroquinolones was about 25%, to aminoglycosides 10%. The resistance to cephalosporins was approximately 55%, to the combination of β-lactam and β-lactamase inhibitors e.g. piperacillin-tazobactam was approximately 40% and to co-trimoxazole 35%. In 13 cases of asymptomatic carrier state antibiotic treatment was not implemented.

Discussion

Infections caused by ESBL (+) pathogens continue to be associated with significant morbidity and mortality worldwide [16]. The rapid development of resistance mechanisms of ESBL (+) bacteria limits the therapeutic possibilities and increases the cost of treatment. The spread of ESBL (+) strains is an epidemiological risk for patients by prolonging the hospital stay and increasing mortality, as well as for hospitals by causing the necessity of expensive antibiotics usage [1, 4].

Urinary tract infections (UTI) are after respiratory tract infections the second most common type of infection affecting children [6]. By the age of 7 up to 8.4% of girls and 1.7% of boys have

| Variable                     | Value       |
|------------------------------|-------------|
| Age [years]:                 |             |
| ≤ 1                          | 30.4% (14)  |
| 1–5                          | 26.1% (12)  |
| > 5                          | 43.5% (20)  |
| Sex:                         |             |
| Female                       | 65.2% (30)  |
| Male                         | 34.8% (16)  |
| Severity of infection:       |             |
| Mild                         | 100% (46)   |
| Prior hospitalizations       | 76.1% (35)  |
| Prior invasive procedures on urinary tracts | 60.9% (28) |
| Urinalysis:                  |             |
| Normal                       | 43.5% (20)  |
| Leucocyturia                  | 56.5% (26)  |
| Urinary tract structural and functional abnormalities | 71.7% (33) |
| Non-urinary chronic diseases | 28.3% (13)  |
| Result of the treatment:     |             |
| Discharged in a good clinical state | 100% (46) |

| Causative factor | Infections |
|------------------|------------|
| Escherichia coli | 43.5% (20) |
| Klebsiella pneumoniae | 36.9% (17) |
| Klebsiella oxytoca | 8.7% (4)  |
| Enterobacter cloacae | 6.5% (3)  |
| Proteus mirabilis | 2.2% (1)   |
| Escherichia coli + Klebsiella pneumoniae | 2.2% (1) |

| Antibiotic                      | Cases       |
|---------------------------------|-------------|
| Cefuroxime                      | 19.6% (9)   |
| Amikacin                        | 8.7% (4)    |
| Amoxicillin with clavulanic acid | 6.5% (3)   |
| Furazidine                      | 6.5% (3)    |
| Ceftiraxone                     | 4.3% (2)    |
| Cephalexin                      | 2.2% (1)    |
| Ofloxacin                       | 2.2% (1)    |
| Co-trimoxazole                  | 2.2% (1)    |
| More than one                   | 19.6% (9)   |
| Not used                        | 28.2% (13)  |

Table I. Characteristics of the study group (n = 46)

Table II. Etiology of ESBL (+) infections

Table III. Antibiotics used in course of treatment
been diagnosed with UTI at least once [5, 6]. Numerous factors which predispose children to UTI have already been defined. The most important of them are structural and functional abnormalities of the urinary tract such as vesicoureteral reflux, short urethra in girls and narrow foreskin of male infants [5, 6]. Furthermore, UTI is the most common infection caused by ESBL (+) bacteria, but we have limited knowledge regarding the clinical epidemiology of these infections. Although well characterized in adults, risk factors, outcomes, therapies, and control measures for ESBL (+) bacteria are less appreciated in children [16].

Reports regarding risk factors for infection or colonization by ESBL (+) bacteria in children were mostly obtained from pediatric intensive care units and neonatal intensive care units. The reports described younger gestational age, low birth weight, prolonged mechanical ventilation, length of hospital stay, invasive devices, and antibiotic use, and maternal-child transmission as the most common risk factors of the ESBL (+) infections. Most studies emphasized that beyond the neonatal period ESBL (+) pathogen infection risk factors for children and adults are similar (e.g. foreign travel, recent UTI, recent antibiotic treatment, numerous hospitalizations, intrafamilial transmission) [17–24]. However, a two-center case-control study of ESBL (+) infection risk factors in children from Chicago identified underlying neurological conditions as a potential risk factor specific to children [25–27]. The same correlation was observed in our study.

Our study revealed urinary tract instrumentation as a potential risk factor of ESBL (+) infection or colonization. To our knowledge, this correlation has not been reported in English literature yet.

The analysis of our results revealed a fivefold increase in ESBL (+) pathogens isolated in microbiological tests during the observed period (2011–2015). Other studies analyzing the results of microbiological tests in terms of isolation of priority pathogen frequency also showed a significant increase in the percentage of isolation of ESBL (+) strains over the last 20 years [3, 8, 12, 28]. A multicenter study carried out in Spain in 2000 (GEIH-BLEE Project 2000) and 2006 (GEIH-project BLEE, 2006) showed an eightfold increase in ESBL (+) infections with *E. coli* and a twofold increase in ESBL (+) infections with *K. pneumoniae* [29]. An analysis of microbiological tests performed by Samet et al. in patients of all departments of a hospital in Gdansk (Poland) conducted in 2001–2003 showed that the frequency of isolation of ESBL (+) did not change significantly during the period, and ranged from 3% to 4.5%. However, in 1999 this incidence was 1.6%, while in 2001 it was 3.2%. The authors of the study suspect that these results may be caused by hospitalizations of asymptomatic carriers [9]. The problem of bacterial ESBL (+) infection in the Pediatrics, Nephrology and Allergology Department of the Military Medical Institute in Warsaw in 2011–2015 concerned from 2.8% to 8.8% of all patients who underwent microbiological tests. The incidence was comparable to the data available in the literature [4, 8, 9].

Nearly half of the children with isolated priority uropathogens were asymptomatic carriers. The results of urine cultures of these patients were obtained after patients’ discharge. It was recommended to perform control urine culture. In the case of re-cultured priority pathogens, treatment should be considered. Carrier state of ESBL (+) strains was mainly associated with previous long-term stays in hospitals, which correlates with our findings [16, 30–33]. Treatment should be considered individually, because antibiotic therapy may promote antibiotic resistance and predispose to symptomatic infection [34, 35].

The source of ESBL (+) bacteria presence in the human organism has not been definitively identified yet. The antibiotics used for humans are also used in veterinary medicine, agriculture and in the livestock breeding [36]. Therefore, food-producing animals and foods of animal origin are under suspicion for being transmission vectors for colonization and infection of humans with ESBL (+) *Enterobacteriaceae* [37, 38].

ESBL (+) bacteria have become a leading antibiotic-resistant threat in children. Options for treatment of ESBL (+) bacterial infections are limited, given that fewer antibiotics are approved for use in children [1]. ESBL (+) strains frequently possess co-resistance genes conferring resistance to aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole, among others, limiting therapeutic options, especially with oral agents [12, 16]. In our study the susceptibility to fluoroquinolones was about 75%, and to aminoglycosides 90%, which was good news in the light of decreasing sensitivity noted worldwide. Therefore, these two groups can be considered as possible therapeutic options in the future.

In conclusion, the results confirm the rising trend of the ESBL (+) infections among hospital-acquired infections during the observed period. ESBL (+) bacteria were isolated primarily in previously hospitalized children with particular reference to urinary tract instrumentation during hospitalizations. The study showed that patients with urogenital disorders and other chronic diseases are more susceptible to these priority pathogen infections. Each bacterial ESBL (+) infection requires cooperation between clinicians, microbiologists, and hospital epidemiologists. This allows for early detection of epidemics and the implementation of appropriate action. The epidemiological surveillance of colonized patients is crucial for the prevention of local epidemics.
The study provides an analysis of multiple cases of ESBL (+) bacteria infections and reveals the most important infection risk factors and treatment options. However, the study was performed in a nephrological department that determines the type of ESBL (+) pathogen infections involved in the analysis. More studies are needed to assess the incidence and virulence of ESBL (+) bacteria that might be accomplished by analyzing data from different departments.

Acknowledgments
We would like to thank the head of the Department of Laboratory Medicine, Military Medical Institute Wiesław Piechota and especially the Microbiology Department for close cooperation with the Department of Pediatrics, Nephrology and Allergology. It was a great help for us, enabling a rapid therapeutic response.

Conflict of interest
The authors declare no conflict of interest.

References
1. Hsu AJ, Tamma PD. Treatment of multidrug-resistant Gram-negative infections in children. Clin Infect Dis 2014; 58: 1439-48.
2. Canton R, Gonzalez-Alba JM, Galan JC. CTX-M enzymes: origin and diffusion. Front Microbiol 2012; 3: 110.
3. Emery CL, Weymouth LA. Detection and clinical significance of extended-spectrum beta-lactamases in a tertiary-care medical center. J Clin Microbiol 1997; 35: 2061-7.
4. Wierzbka J, Rybak B, Bronk M, et al. Nosicielstwo i zakażenia pacleczkami z rodziny Enterobacteriaceae wytwarzającymi szeroko spektralne beta-laktamazy ESBL u pacjentów Oddziału Niemowlęcego Kliniki Pediatrii, Hematologii, Onkologii i Endokrynologii Gdańskiego Uniwersytetu Medycznego w latach 2002-2005. Ann Acad Med Gedan 2009; 39: 155-62.
5. Megged O. Extended spectrum beta-lactamase-producing bacteria causing community acquired urinary tract infections in children, Pediatr Nephrol 2014; 29: 1583-7.
6. Marcus N, Ashkenazi S, Samra Z, Cohen A, Livni G. Community-acquired enterococcal urinary tract infections in children. Pediatr Nephrol 2012; 27: 109-14.
7. Abraham E, Chain E. An enzyme from bacteria able to destroy penicillin. Nature 1940; 146: 837-7.
8. Samet A, Bronk M, Czarniak E, et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in children: old foe, emerging threat. Clin Infect Dis 2015; 60: 1389-97.
9. Leverstein-van Hall MA, Dierixx CM, Cohen Stuart J, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin Microbiol Infect 2011; 17: 873-80.
10. Bush K, Jacoby GA. Updated functional classification of extended-spectrum beta-lactamase producing organisms. J Infect 2009; 73: 345-54.
11. Rawat D, Nair D. Extended-spectrum beta-lactamases in Gram negative bacteria. J Global Infect Dis 2010; 2: 263-74.
12. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 2005; 18: 657-86.
13. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 20th informational supplement. M100-S20. Wayne, PA: CLSI, 2010.
14. Falagas M, Karageorqopoulos D. Extended spectrum beta-lactamase producing organisms. J Infect 2009; 73: 345-54.
15. Hawkey P, Jonem A. The changing epidemiology of resistance. J Antimicrob Chemother 2009; 64 (suppl 1): i3-10.
16. Lukac P, Bonomo R, Logan L. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in children: old foe, emerging threat. Clin Infect Dis 2015; 60: 1389-97.
17. Leverstein-van Hall MA, Dierixx CM, Cohen Stuart J, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin Microbiol Infect 2011; 17: 873-80.
18. Laupland KB, Church DL, Vidakovich I, Mucenski M, Pitoud JT. Community-onset extended-spectrum beta-lactamase (ESBL) producing Escherichia coli: importance of international travel. J Infect 2008; 57: 441-8.
19. Tande D, Boisrame-Gastrin S, Munch MR, et al. Intrafamilial transmission of extended-spectrum-beta-lactamase-producing Escherichia coli and Salmonella enterica Babelsberg among the families of internationally adopted children. J Antimicrob Chemother 2010; 65: 859-65.
20. Dayan N, Dabbah H, Weissman I, Aga I, Even L, Gilman D. Urinary tract infections caused by community-acquired extended-spectrum beta-lactamase-producing and nonproducing bacteria: a comparative study. J Pediatr 2013; 163: 1417-21.
21. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase producing Escherichia coli and Klebsiella species in children. Pediatrics 2005; 115: 942-9.
22. Jhaveri R, Bronstein D, Sollod J, Kitchen C, Krogsstad P. Outcomes of infections with extended spectrum beta-lactamase producing organisms in children. J Pediatr Infect Dis 2008; 3: 229-33.
23. Blaschke AJ, Korgenski EK, Daly JA, LaFleur B, Pavia AT, Byington CL. Extended-spectrum beta-lactamase-producing pathogens in a children’s hospital: a 5-year experience. Am J Infect Control 2009; 37: 435-41.
24. Jaworski R, Haponiuk I, Steffens M, et al. Colonization of multidrug resistant pathogens in a hybrid pediatric cardiac surgery center. Arch Med Sci 2016; 12: 639-44.
25. Logan KL, Meltzer LA, McAuley JB, et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae infections in children: a two-center case-case-control study of risk factors and outcomes in Chicago, Illinois. J Pediatr Infect Dis Soc 2014; 3: 312-9.
26. Fan NC, Chen HH, Chen CL, et al. Rise of community-onset urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli in children. J Microbiol Immunol Infect 2011; 44: 399-405.
27. Topaloglu R, Er I, Dogan BG, et al. Risk factors in community-acquired urinary tract infections caused by ESBL-producing bacteria in children. Pediatr Nephrol 2010; 25: 919-25.
28. Peña C, Gudiel C, Tubau F, et al. Risk-factors for acquisition of extended-spectrum beta-lactamase-producing Escherichia coli among hospitalized patients. Clin Microbiol Infect 2006; 12: 279-84.
29. Angel Díaz M, Ramón Hernández J, Martínez-Martínez L, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in Spanish hospitals: 2nd multicenter study (GEIH-BLEE project, 2006). Enferm Infecc Microbiol Clin 2009; 27: 503-10.

30. Crivaro V, Bagattini M, Salza MF, et al. Risk factors for extended-spectrum beta-lactamase-producing Serratia marcescens and Klebsiella pneumoniae acquisition in a neonatal intensive care unit. J Hosp Infect 2007; 67: 135-41.

31. Rettedal S, Hoyland Lohr I, Natas O, Sundsfjord A, Oymar K. Risk factors for acquisition of CTX-M-15 extended-spectrum beta-lactamase-producing Klebsiella pneumoniae during an outbreak in a neonatal intensive care unit in Norway. Scand J Infect Dis 2013; 45: 54-8.

32. Shakil S, Akram M, Ali SM, Khan AU. Acquisition of extended-spectrum beta-lactamase producing Escherichia coli strains in male and female infants admitted to a neonatal intensive care unit: molecular epidemiology and analysis of risk factors. J Med Microbiol 2010; 59: 948-54.

33. Vijayakanthi N, Bahl D, Kaur N, Maria A, Dubey NK. Frequency and characteristics of infections caused by extended-spectrum beta lactamase-producing organisms in neonates: a prospective cohort study. Biomed Res Int 2013; 2013: 756209.

34. Cardiff-Oxford Bacteriuria Study Group. Sequelae of covert bacteriuria in schoolgirls: a four-year follow-up study. Lancet 1978; 311: 889-93.

35. Verrier Jones K, Asscher AW, Verrier Jones ER, et al. Glomerular filtration rate in schoolgirls with covert bacteriuria. Br Med J 1982, 285: 1307-10.

36. Capita R, Alonso-Calleja C. Antibiotic-resistant bacteria: a challenge for the food industry. Crit Rev Food Sci 2013; 53: 11-48.

37. WHO. Integrated surveillance of antimicrobial resistance: guidance from a WHO Advisory Group. 2013. ISBN 978 92 4 150631 1, Switzerland.

38. Valentin L, Sharp H, Hille K, et al. Subgrouping of ESBL-producing Escherichia coli from animal and human sources: an approach to quantify the distribution of ESBL types between different reservoirs. Int J Med Microbiol 2014; 304: 805-16.