CASE REPORT

Journal of Clinical Microbiology and Infectious Diseases (*JCMID*) 2021, Volume 1, Number 1: 11-15

Published By : the Indonesian Society for Clinical Microbiology

Urinary Tract Infection (UTI) caused by Extended-Spectrum Beta-Lactamase (ESBL)-producing *Enterobacteriaceae*: a case series

Qonita Imma Irfani[1], Dessy Kurnia Sari[1], Dewi Purbaningsih[1], Tri Wibawa[1], Titik Nuryastuti[1*]

[1]Microbiology Department, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

*Corresponding to:
Titik Nuryastuti;
Microbiology Department, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia;
t.nuryastuti@ugm.ac.id

Received: 2021-05-09
Accepted: 2021-06-15
Published: 2021-06-25

ABSTRACT

Introduction: A urinary tract infection (UTI) is an infection in any part of the urinary system, occurring in the kidneys, bladder, ureters, and urethra. UTI incidence in Indonesia was high enough. The prevalence of UTI in the community enhances in line with the increase of age. 40-60 years had a prevalence rate of 3.2%, while at the age of ≥65, a UTI had a prevalence rate of 20%. UTIs are among the most common infections in humans. Enterobacteria that produce extended-spectrum beta-lactamase (ESBL) is one of the most frequent causes Prevalence of the ESBL bacterial infection is developing due to the widespread prescription of antibiotics around the world. Thus, our articles established several UTI cases of various ages and their antibiotic susceptibility.

Case Description: This case report series presents eight cases describing a UTI caused by Enterobacteriaceae producing ESBL in various ages. Data were collected retrospectively from secondary sources of laboratory results. Patient baby-child mostly had a history of sepsis. Other than that patient had hydronephrosis kidney, seizure, fever. On the other hand, the patient's old man and woman had a history of fever, shock spinal and fracture, malignancy. All patients were tested for antibiotic susceptibility and mostly still sensitive with amikacin, meropenem, nitrofurantoin, and fosfomycin.

Conclusions: Our case series established that patients with UTI were mainly still sensitive to amikacin, meropenem, nitrofurantoin, and fosfomycin. We should implement and maintain contact precautions throughout the hospital wards to prevent the transmission of ESBL infections.

Keywords: Urinary tract infection, Enterobacteriaceae, Extended-spectrum beta-lactamase.
Cite This Article: Irfani, Q.I., Sari, D.K., Purbaningsih, D., Wibawa, T., Nuryastuti, T. 2021. Urinary Tract Infection (UTI) caused by Extended-Spectrum Beta-Lactamase (ESBL)-producing *Enterobacteriaceae*: a case series. *Journal of Clinical Microbiology and Infectious Diseases* 1(1): 11-15.

INTRODUCTION

The most common infections reported in outpatient settings are Urinary Tract Infections (UTIs). Approximately 150 million people were infected each year. The incidence increases with age and is associated with high morbidity, mortality, and economic cost. Following the high incidence of respiratory system infections, UTIs are the second most common type of infection. The most common UTI cause in all age groups is *E. coli* (65% to 75%). Other bacteria agents include *Klebsiella* species, usually *Klebsiella pneumoniae* (23%), *Proteus mirabilis* (7%), other Enterobacteriaceae, *Enterococcus* species, *Pseudomonas aeruginosa*, *staphylococcus saprophyticus* (1% to 4%).[1]

Women around 50% will be infected in their life span, and approximately 25% of them suffer recurrent UTIs after six months.[2] Even though statistically, women have a higher prevalence than men, uncircumcised boys have a ten until the twelve-fold increased risk of UTIs rather than girls. It was documented that UTIs infected around 5% of girls. Meanwhile, the circumcised boys were 20%.[3] UTIs incidence in Indonesia was high enough. The prevalence of UTI in the community enhances in line with the increase of age. 40-60 years had a prevalence rate of 3.2%, while at the age of ≥65, a UTI had a prevalence rate of 20%.[4]

Factors that are important to consider in treating UTI are bacterial virulence and host factors.[5] Some bacteria that can cause UTI may not be susceptible to antibiotic treatments, as in the case of some *Enterobacteria* that produce extended-spectrum beta-lactamase (ESBL) that have developed antibiotic resistance. Hospital-acquired infections (HAI), also known as nosocomial infections, have continued to increase in many countries due to the irrational prescribing of antibiotics without appropriate laboratory testing for susceptibility.[1]

Cases of UTI in hospitalized patients that use medical equipment are often more susceptible to infection by common pathogens, including *Escherichia coli* (*E. coli*) and require specific laboratory testing to identify the invading pathogen and determine the results of susceptibility tests for various treatments. *Enterobacteriaceae* spp. are commonly occurring bacteria

that inhabit the human gastrointestinal (GI) tract in humans. These infections are often acquired during their stay in the hospitalization (nosocomial). Generally, *E. coli* is the most common etiology of these nosocomial infections, but it also is the leading cause of community-acquired UTIs.[6]

Urinary tract infections affect more women in both children and adult populations. Currently, the incidence of UTI attributed to antibiotic-resistant bacteria is increasing. Enterobacteria that produce extended-spectrum beta-lactamase (ESBL) is one of the most frequent causes. Prevalence of the ESBL bacterial infection is developing due to the widespread prescription of antibiotics around the world.[7]

Beta-lactamases are enzymes that open the beta-lactam ring to inactivate the antibiotic treatment. According to the type of their substrates, they are classified into four functional groups: penicillinase, extended-spectrum beta-lactamase (ESBL), carbapenemase and cephalosporins type AmpC. This ESBL is found in the Enterobacteriaceae family's specific genera, including *E. coli* and *Klebsiella pneumoniae* and other bacteria like *Haemophilus influenza* and *Pseudomonas aeruginosa*. ESBL arises mainly due to mutation in β-lactamases encoded by the *blaSHV*, *blaTEM*, and *blaCTX-M* genes.[8–10]

Table 1 shows the detail of patients list suffering from UTI and infected by ESBL *Enterobacteriaceae* will explain the criteria of the sample, such as age, sex, type of *Enterobacteriaceae* that causes infection. The sampling period starts from January 2020 to December 2020.

Table 1. Patient characteristics suffering from UTI

Patient	Age (years)	Gender	ESBL Species
1	1	Female	*Klebsiella pneumonia*
2	2	Female	*Escherichia coli*
3	1	Male	*Serratia marcescens*
4	40	Male	*Enterobacter cloacae*
5	16	Female	*Escherichia coli*
6	60	Female	*Escherichia coli*
7	1	Male	*Escherichia coli*
8	63	Female	*Klebsiella pneumonia*

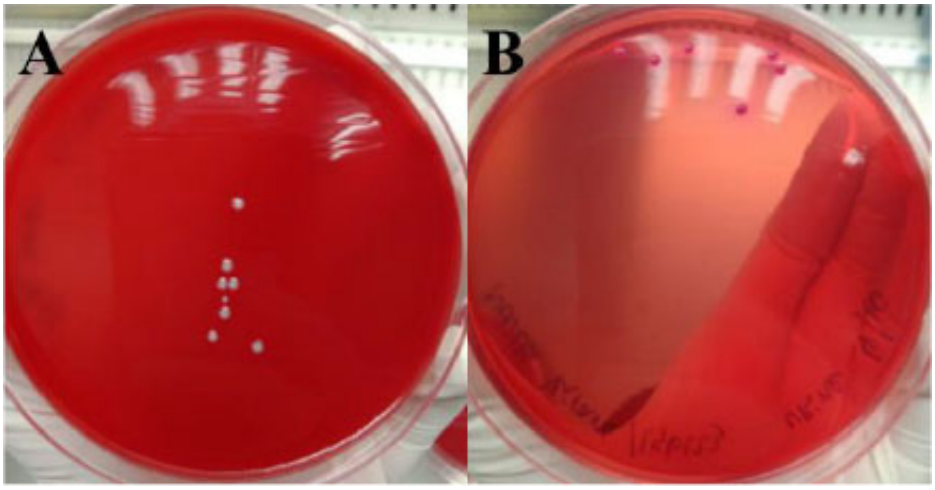

Figure 1. Urine Culture in Blood Agar Medium (A) in Mac Conkey Agar Medium (B)

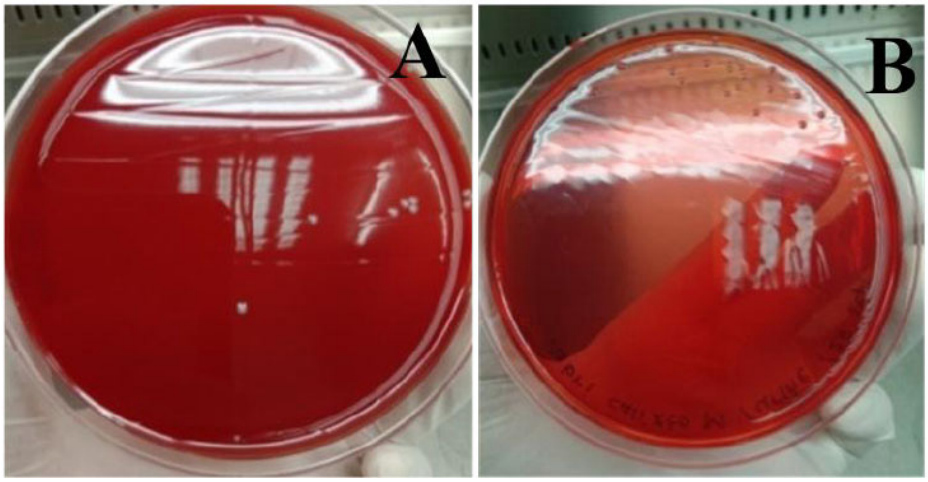

Figure 2. Urine Culture in Blood Agar Medium (A) in Mac Conkey Agar Medium (B).

CASE DESCRIPTION

Case 1

A 10-month-old baby girl was taken to hospital with a high fever two days ago. The patient also had diarrhea three times a day. No complaints of nausea, vomiting, coughs and colds. When she was neonatal, patients had a history of sepsis, neonatal dehydration, hyperbilirubinemia, hypernatremia and urinary tract infections. Physical examination obtained temperature 39.7°C, breath 24x/mnt, heart rate 157-160x/mnt, and weight 9.8 kg. Routine blood test obtained leukocyte count 9.200/uL, hemoglobin 7,9 g/dL and platelets 554.000/uL. Urine culture examination found *Klebsiella pneumoniae* ESBL with bacterial count 5.5 X 10^3 CFU/ml. The bacteria were still sensitive to Amikacin, Levofloxacin and Fosfomycin.

Case 2

A child aged one year and two months were referred to the hospital with sepsis and anemia. The child had a fever one week before. Since two days before, she had been getting medication from the public health center, such as paracetamol and amoxicillin. The patient had chief

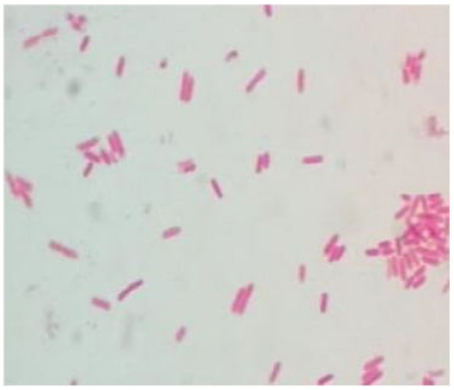

Figure 3. Gram Staining of *E. coli*

complaints regarding urination and defecation. She also had a history vomited twice. On a routine blood test, the leukocyte count was 9,1 g/dl. The urine laboratory examination found leukocyte esterase was 500l eu/u, and the leukocyte count was 17-20 cell/lpb. *Escherichia coli* ESBL (figure 1) was obtained from urine culture with the bacterial count was 7 x 10^2 CFU/ml. *Escherichia coli* ESBL, in this case still sensitive to Amikacin, Meropenem, and Piperacillin/Tazobactam.

Case 3

A one-year-old boy has been admitted to the hospital with the chief complaint of persistent fever with dehydration. On a routine blood test, the leukocyte count was 20,4 g/dl. The urine laboratory examination found cloudy urine, positive bacteriuria and urinary leukocytes 30-35 cell/lpb. In urine culture, the germ count was 1,1 x 10^2 CFU/ml. The result of urine culture showed the growth of *Serratia marcescens*-ESBL (figure 2) and still sensitive to Amikacin, Meropenem, Nitrofurantoin and Fosfomycin.

Case 4

A 40 years old man was referred from a secondary hospital with spinal shock and fracture. He was hospitalized in ICU because of unconsciousness as an effect of spinal cord injury and paraplegic fracture L1. For one month, he was hospitalized, from urine laboratory tests found bloody urine, leukocyte positive and bacteriuria. Urine culture had been done, with the germ count was >10^5 CFU/ml, the result was *Enterobacter cloacae* ESBL, that is susceptible in Meropenem and Fosfomycin using Vitek2.

Case 5

A 15 years girl with a hydronephrosis kidney has been hospitalized and got treatment with surgery. On laboratory testing, cloudy urine was found with bacteriuria, and there was leukocytosis (9.9x10^3/ul) from a blood test. In urine culture, the germ count 1.5x10^7 CFU/ml, and the Vitek2 identification result was *Escherichia coli* ESBL that susceptible in Amikacin, Meropenem, Tigecycline, Piperacillin-Tazobactam and Nitrofurantoin.

Case 6

A 60-year-old woman came to the hospital because there was weakness on one side of the body, difficulty speaking, urinating and defecating. The patient was a patient with diabetes mellitus and uncontrolled hypertension. There was cloudy urine on the urine examination, and the urine germ count was more than 10^5 CFU / ml. The urine culture showed the growth of *E. coli* ESBL (figure 3) that were still susceptible to Amikacin, Nitrofurantoin and Tigecycline.

Case 7

A 7-month-old baby was taken to the hospital for a 5-minute seizure. The patient had a fever five days before no complaints of coughs, colds, urination and defecation. Routine blood tests found the number of leukocytes 11,000/uL. In routine urine examination, leukocyte esterase results in 250 leu/uL, leukocytes 10-15 cells/lpb. The urine culture showed the gowth of *E. coli* ESBL bacteria with germ numbers of 1.7 x 10 CFU/ml. Bacteria were still sensitive to Amikacin, Nitrofurantoin, and Tigecycline usingVitek2.

Case 8

A 63-year-old woman was admitted to the hospital because of unconsciousness with a high fever and cough. She was a bedridden patient with a history of cancer metastases to the brain. In blood culture, there was no growth. Whereas on urine examination, cloudy urine was found, the colony count was more than 10^5 CFU/ml, and urine culture showed the growth of *Klebsiella pneumoniae* bacteria with ESBL that were still sensitive to Amikacin, Levofloxacin, Nitrofurantoin and Fosfomycin.

DISCUSSION

Urinary tract infections are the most common bacterial infections in the community and hospital settings, causing severe health threats to children and vulnerable populations. *Escherichia coli* and *Klebsiella* species are the most common pathogens. They have varying antimicrobial resistance mechanisms that may include the production of extended-spectrum b-lactamase (ESBL).[11,12] *Escherichia coli* and *Klebsiella* species are found in specific genera of the *Enterobacteriaceae* family, including *Escherichia coli* and *Klebsiella pneumoniae* and other bacteria such as *Haemophilus influenzae* and *Pseudomonas aeruginosa.*[4] Our study shows that women are more susceptible to UTI than men due to the differences in the anatomy in both eliminatory and reproductive systems. In women, the most periurethral and vaginal areas promote the growth of uropathogenic. The shorter urethral length increases the chance for ascending infection into the urinary tract, consistent with Ramadan et al.[7]

The risk factors of UTIs are gender, premenopausal women, patients with a history of diabetes, neurogenic bladder, spinal cord injury, pregnancy, prostatic hypertrophy, patient with catheters more than 30 days, and age.[13] According to our case series patients with UTI was in varies age and mostly female. Other case series established that female UTI patients were 80.33± 7.69 years old.[14] Difference risk factors have different outcomes. A clinical study established that elderly with diabetes mellitus and dementia increase the risk of mortality in elderly UTI patients.[15] Whereas, children with UTIs must be given the antibiotic as soon as possible to get a better prognosis.[16]

Collecting the urine specimen to give the appropriate antibiotic is needed. The patient's urine sampling is easily contaminated with the microbiota of the perineum, urethra, or vagina. Meanwhile, colony counts are essential in establishing the microbiological significance of bacteriuria. Therefore urine culture is always reported with the number of

colonies accompanying it.[17] In our cases, we found four cases with *E.coli* ESBL, two cases with *K.pneumoniae* ESBL and two cases with *S.marcescens* ESBL and *E.cloacae* ESBL, respectively. There was variation in CFU. Three cases showed low colonies in urine cultures ($5.5x10^3$, $7x10^2$, $1.1x10^2$), and the others are $>10^4$. The ESBL UTIs were affected in four adults (three women, one man, respectively) and four children (two boys, two girls, respectively), as seen in the table.

Colony count $\geq 10^5$ CFU/ml shows significant bacteriuria in most specimens submitted for culture. However, it should be noted that mixed cultures in uncomplicated outpatient populations are likely to indicate contamination. Nevertheless, colony counts of $<10^5$ CFU/ml from patients with dysuria and UTI symptoms may be significant. Low levels ($<10^4$ CFU/ml) of organisms commonly found in the skin and external and internal genitalia are considered contaminants, but, in specified circumstances, Enterobacteriaceae count of 10^2 CFU/ml or more, especially for Salmonella, can be considered significant.[17]

Interestingly, we found UTI ESBL in hospitalized patients, especially in children. Childhood UTIs may cause increased morbidity, hospitalization and long-term clinical consequences like renal scars, hypertension and chronic kidney damage.[6,12] As ESBL infections have been reported increasingly worldwide. This condition makes us have to be aware of the possibility of ESBL transmission in our hospital.

Some risk factors can induce ESBL infections in UTI, i.e., using a urinary catheter, antibiotic exposure like cephalosporin before hospital admission, and need for admission in ICU.[10,11,18] There would be procedures to be done to prevent this infection. Szel et al. have been reported that some procedures could decrease the ESBL transmission in the intensive care unit, as follow: 1) Hand hygiene compliance among healthcare workers, 2) Modified antibiotic protocol, 3) Progressive feeding for neonates, 4) A saving bather protocol, 5) Identify potential reservoirs and risk factors, environmental screening was performed, and samples were taken from various surfaces more intensive (every half month), 6) Quality cleaning and disinfection, 7) Screening ESBL for a new patient with a rectal swab.[19,20]

Several factors in hospital settings cause HAI to spread between patients rapidly. These include close contact with medical personnel, instrumentation used in examinations, medical equipment (such as iv lines, ventilator, and urine catheter) and standard exit and entry areas. For example, using door handles, sink basins, and railings going up and down steps provide an ideal opportunity to transmit pathogens. Additionally, the moist environment in bathrooms contributes to the rapid spread of this nosocomial infections.[18]

The organisms producing ESBL can hydrolyze penicillin, broad-spectrum cephalosporins, and monobactams, but they do not affect the cephamycins or carbapenems clavulanic acid inhibit their activity. In addition, ESBL-producing organisms are frequently exhibiting resistance to other antimicrobial classes such as fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole due to associated resistance mechanisms, which may be either chromosomally or plasmid-encoded. Widespread use of third-generation cephalosporin was believed to be the primary cause of mutations in these enzymes, leading to the emergence of plasmid-encoded ESBLs. ESBLs were transferred between bacteria by plasmids spread by clonal distribution between hospitals and countries through patient mobility.[21]

CONCLUSIONS

Our case series established that patients with UTI were mostly still sensitive with amikacin, meropenem, nitrofurantoin, and fosfomycin. We should implement and maintain contact precautions throughout the hospital wards to prevent the transmission of ESBL infections. It is also necessary to regularly carry out hospital environment surveillance from high-risk units for early identification of ESBL colonization. Hand hygiene is the most crucial step for all healthcare workers, and best practice monitoring could help reduce the risk of ESBL transmission.

DISCLOSURE

Funding
No funding.

Ethical Approval
The study is exempt from ethical approval in our institution.

Conflict of Interest
There is no conflict of interest in this study.

Author Contributions
Conceptualization, methodology and writing original draft preparation: Nuryastuti T; Formal analysis: Irfani Q, Sari D, Purbaningsih D; Data curation: Irfani Q, Sari D, Purbaningsih D; Validation: Wibawa T; Writing, review and editing: Sari D, Irfani Q; Approval of final manuscript: all authors.

ACKNOWLEDGEMENT

The authors would like to thank Mega, Laely, Laili and Apri for obtaining the isolates. We also thank all Klinik Bahasa staff in the Faculty of Medicine Gadjah Mada Univercity for editing this journal.

REFERENCES

1. Mandell GL, Douglas RG, Bennet JE. PREFACE TO THE FIRST EDITION [Internet]. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier; 2010. p. xxvii. Available from: http://dx.doi.org/10.1016/b978-0-443-06839-3.00333-7
2. McLellan LK, Hunstad DA. Urinary Tract Infection: Pathogenesis and Outlook. Trends Mol Med. 2016;22(11):946–57.
3. Leung AKC, Wong AHC, Leung AAM, Hon KL. Urinary Tract Infection in Children. Recent Pat Inflamm Allergy Drug Discov. 2019;13(1):2–18. Available from: https://pubmed.ncbi.nlm.nih.gov/30592257
4. Sasongkowati R, Chitraningtyas D, Christyaningsih J. Research Journal of Pharmaceutical, Biological and Chemical Sciences The Study on the Susceptibility of Enterococcus faecalis and Klebsiella ozaenae Cause UTI to Antibiotics in East Java, Indonesia. 6(1539):1539–44.
5. Southwick FS. Infectious Diseases: A Clinical Short Course, 4th Edition [Internet]. McGraw-Hill Education; 2020. Available from: https://books.google.co.id/books?id=D7J3wwEACAAJ
6. Tille PM. Bailey & Scott's Diagnostic Microbiology [Internet]. Elsevier; 2014. Available from: https://books.google.co.id/books?id=tfx7MAEACAAJ
7. Ramadan DS, Bassyoni EA, Amer MM. Detection of ESBL Producing Bacteria in Cases of Urinary Tract Infection in Pediatric

Department at Benha University Hospital. Egypt J Med Microbiol. 2016;25(1):77–84. Available from: http://dx.doi.org/10.12816/0037095
8. Gharavi MJ, Zarei J, Roshani-Asl P, Yazdanyar Z, Sharif M, Rashidi N. Comprehensive study of antimicrobial susceptibility pattern and extended spectrum beta-lactamase (ESBL) prevalence in bacteria isolated from urine samples. Sci Rep. 2021;11(1). Available from: http://dx.doi.org/10.1038/s41598-020-79791-0
9. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. J Chemother. 2017;29(sup1):2–9. Available from: http://dx.doi.org/10.1080/1120009x.2017.1380395
10. Al-Jamei SA, Albsoul AY, Bakri FG, Al-Bakri AG. Extended-spectrum β-lactamase producing E. coli in urinary tract infections: A two-center, cross-sectional study of prevalence, genotypes and risk factors in Amman, Jordan. J Infect Public Health. 2019;12(1):21–5. Available from: http://dx.doi.org/10.1016/j.jiph.2018.07.011
11. Albaramki JH, Abdelghani T, Dalaeen A, Khdair Ahmad F, Alassaf A, Odeh R, et al. Urinary tract infection caused by extended-spectrum β-lactamase-producing bacteria: Risk factors and antibiotic resistance. Pediatr Int. 2019;61(11):1127–32. Available from: http://dx.doi.org/10.1111/ped.13911
12. Vachvanichsanong P, McNeil EB, Dissaneewate P. Extended-spectrum beta-lactamase Escherichia coli and Klebsiella pneumoniae urinary tract infections. Epidemiol Infect. 2020;149. Available from: http://dx.doi.org/10.1017/s0950268820003015
13. Gupta K, Grigoryan L, Trautner B. Urinary Tract Infection. Ann Intern Med. 2017;167(7):ITC49–64.
14. Chernyak S, Salamon C. Intravesical Antibiotic Administration in the Treatment of Recurrent Urinary Tract Infections: Promising Results From a Case Series. Female Pelvic Med Reconstr Surg. 2020;26(2):152–4.
15. Kakde P, Redkar NN, Yelale A. Urinary Tract Infection in Elderly: Clinical Profile and Outcome. J Assoc Physicians India. 2018;66(6):14–7.
16. Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJM, Radmayr C, et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015;67(3):546–58.
17. Gerber BH, Ohd A. Zur Diagnostik von Harnwegsinfektionen im Woch enbett. 1994;54:524–8.
18. Woerther P-L, Burdet C, Chachaty E, Andremont A. Trends in Human Fecal Carriage of Extended-Spectrum -Lactamases in the Community: Toward the Globalization of CTX-M. Clin Microbiol Rev. 2013;26(4):744–58. Available from: http://dx.doi.org/10.1128/cmr.00023-13
19. Goyal D, Dean N, Neill S, Jones P, Dascomb K. Risk Factors for Community-Acquired Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae Infections—A Retrospective Study of Symptomatic Urinary Tract Infections. Open Forum Infect Dis. 2019;6(2). Available from: http://dx.doi.org/10.1093/ofid/ofy357
20. Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. J Antimicrob Chemother. 2016;71(10):2729–39. Available from: http://dx.doi.org/10.1093/jac/dkw221
21. Abayneh M, Tesfaw G, Abdissa A. Isolation of Extended-Spectrum β-lactamase- (ESBL) Producing Escherichia coli and Klebsiella pneumoniae from Patients with Community-Onset Urinary Tract Infections in Jimma University Specialized Hospital, Southwest Ethiopia. Can J Infect Dis Med Microbiol. 2018;2018:1–8. Available from: http://dx.doi.org/10.1155/2018/4846159