

Outcome of urinary tract infection caused by Extended Spectrum Beta-Lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae* in Dr Zainoel Abidin General Hospital Aceh



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ABSTRACT

Introduction: Extended-spectrum β -lactamase (ESBL) is a mutated β -lactamase enzyme that can hydrolyze beta-lactam antibiotics. The aim of this study was to determine the incidence rate, characteristics of patients, antibiotic use and outcome of urinary tract infections (UTIs) due to ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* at Dr Zainoel Abidin General Hospital Aceh.

Method: The samples of this study were all *Escherichia coli* and *Klebsiella pneumoniae* isolated from urine culture of UTI cases. Patient characteristics and antibiotic use data were extracted from medical records. UTIs outcome was assessed as clinical improvement or death within a maximum of 30 days of treatment.

Result: The results of this study obtained 63 patients with UTIs caused by *E. coli* and *K. pneumoniae* of which 52.4% of them were ESBL producers. The incidence of UTIs due to *E. coli* was higher than that of *K. pneumoniae*, 63.5% and 36.5% respectively. *E. coli* ESBL producers were more in number than non-ESBL, conversely *K. pneumoniae* were mostly non-ESBL. The characteristics of patients with UTIs caused by *E. coli* and *K. pneumoniae* were predominant women 52.4%, and most cases were at 56-64 years old. Antibiotic therapy that given before and after culture results to UTI patients were generally ceftriaxone. UTIs outcome due to ESBL producing *Escherichia coli* and *Klebsiella pneumoniae* showed that 26/33 (78.8%) patients experienced improvement, however, 7/33 (21.2%) patients died.

Conclusion: The irrational use of ceftriaxone in patients with UTI caused by ESBL producing *E. coli* and *K. pneumoniae* has led to a poor outcome for the patient.

Keywords: Ceftriaxone, ESBL, *Escherichia coli*, *Klebsiella pneumoniae*, UTI.

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INTRODUCTION

Urinary tract infections (UTIs) is an infection caused by microbes, including Gram-positive or Gram-negative bacteria.¹ Most of the pathogenic bacteria are in the Gram-negative group and 76% belong to the *Enterobacteriaceae* family, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus*, *Enterobacter*, and family of *Pseudomonaceae*, such as *Pseudomonas sp.* as well as other *Proteaceae*. *E. coli* bacteria were found in 28% of cases of UTI and *K. pneumoniae* in 26%.²

Several species of *Enterobacteriaceae* can carry out mutations that produce Extended-Spectrum Beta-Lactamase (ESBL), an enzyme that hydrolyzes most of the beta-lactam

antimicrobials. ESBL producing genes can be passed via reproduction or can be transferred from one to another. Species which produce ESBL are *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *Proteus mirabilis*.³

The emergence of ESBL bacteria poses challenges in the choice of therapy which may prolong the use of antibiotics, length of stay in the ICU, aggravating the disease, and use of invasive medical devices. Furthermore, the uncertain treatment is due to the limited selection of antibiotics used. Infection by ESBL-producing bacteria can usually be found in a hospital, for example, urinary tract infections.^{4,5}

Studies in 5 different hospitals in Indonesia in 2013 showed that the prevalence rate of ESBL

bacteria was 32-68%. This shows that the health care system in Indonesia is facing a serious problem in dealing with infectious disease.⁶ A previous study in Dr Zainoel Abidin Hospital found that most of *E. coli* and *K. pneumoniae* were ESBL-producing bacteria. Approximately 89% ESBL *E. coli* were found in 38 isolates, while ESBL *K. pneumoniae* were found in 48 (81%) of 59 isolates. ESBL *E. coli* and ESBL *K. pneumoniae* are resistant to third-generation cephalosporin but are generally sensitive to amikacin and meropenem.⁷

ESBL-producing *E. coli* and *K. pneumoniae* are able to inhibit the action of various kinds of antibiotics. This study aims to determine the incidence rate, the patient's characteristics, the use of antibiotics, and the outcome of UTIs due to ESBL-producing *E. coli* and *K. pneumoniae* at Dr Zainoel Abidin Hospital in Banda Aceh.

MATERIAL AND METHODS

This study was conducted at the General Hospital in Banda Aceh, Dr Zainoel Abidin Hospital, during the periods of August to December 2018. Samples were collected from the urine samples of patients with UTIs caused by *E. coli* and *K. pneumoniae* during inpatient treatment. The isolates were cultured on MacConkey agar in the laboratory of Microbiology at Dr Zainoel Abidin Hospital. Bacterial identification, antibiotics sensitivity test, and ESBL determination were carried out using Vitex-2 compact. Patient characteristics data and the use of antibiotic therapy were taken from medical records. UTIs outcomes were assessed as recovery or death within 30 days of treatment.

RESULTS

The incidence rate of UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae*.

The incidence rate of UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae* at Dr Zainoel Abidin Hospital is 52.4%. Table 1 below also shows that the incidence of UTIs caused by *E. coli* (63.5%) is higher than *K. pneumoniae* (36.5%). UTIs caused by *E. coli* were found much higher from the ESBL-producing group (60%) than non-ESBL one (40%).

Table 1. The incidence rate of UTIs caused by *E. coli* and *K. pneumoniae*

Specimens	Characteristic of Bacteria	ESBL	Non ESBL	Total
Urine	<i>E.coli</i>	24 (60%)	16 (40%)	40 (63.5%)
	<i>K. pneumoniae</i>	9 (39.1%)	14 (60.9%)	23 (36.5%)
	Total	33 (52.4%)	30 (47.6%)	63 (100%)

Table 2. Patient Characteristics by Gender

Bacterial Characteristic	Isolate	Male	Female	Total
<i>E. coli</i>	ESBL	8 (24.2%)	16 (48.5%)	24 (38.1%)
	Non ESBL	7 (30%)	9 (23.3%)	16 (25.4%)
<i>K. pneumoniae</i>	ESBL	6 (18.2%)	3 (9.1%)	9 (14.1%)
	Non ESBL	9 (30%)	5 (16.7%)	14 (22.2%)
Total		30 (47.6%)	33 (52.4%)	63 (100%)

Table 3. Patient Characteristics by Age

Age	Isolate	ESBL	Non ESBL
18-25 years	<i>E. coli</i>	1 (3.03%)	2 (6.67%)
	<i>K. pneumoniae</i>	0	2 (6.67%)
26-35 years	<i>E. coli</i>	2 (6.06%)	3 (10.00%)
	<i>K. pneumoniae</i>	1 (3.03%)	0
36-45 years	<i>E. coli</i>	6 (18.18%)	3 (10.00%)
	<i>E. coli</i>	6 (18.18%)	1 (3.33%)
46-55 years	<i>K. pneumoniae</i>	5 (15.15%)	2 (6.67%)
	<i>E. coli</i>	9 (27.27%)	7 (23.33%)
56-64 years	<i>K. pneumoniae</i>	3 (9.10%)	10 (33.33%)
	Total	33 (100%)	30 (100%)

Table 4. Total of Empiric Use of Antibiotics

Antibiotics	n/N	Percentage(%)
Ceftriaxone	27/33	58.6
Cefoperazone	6/33	13.0
Meropenem	1/33	2.2
Levofloxacin	2/33	4.3
Cefazolin	1/33	2.2
Cefixime	2/33	4.3
Cefotaxime	1/33	2.2
Ciprofloxacin	1/33	2.2
Doxycycline	1/33	2.2
Kotrimoksazol	1/33	2.2
Metronidazole	1/33	2.2
Ofloxacin	1/33	2.2
Vancomycin	1/33	2.2
Total	46/33	100

Meanwhile, the incidence of UTIs caused by *K. pneumoniae* were dominant from the non-ESBL group (60.9%).

Patient Characteristics by Gender

During the period of study, 63 patients whom diagnosed with UTIs caused by *E. coli* and *K. pneumoniae* at Dr Zainoel

Abidin Hospital manifest more in female (52.4%) with a ratio of 33 to 30 male (Table 2).

Patient Characteristics by Age

UTIs caused by *E. coli* and *K. pneumoniae* generally occurs at the age of 56-64 years with a total of 29 (46.03%) patients.

Table 5. Percentage of Definitive Use of Antibiotics

Antibiotics	n/N	Percentage (%)
Ceftriaxone	5/33	25
Cefoperazone	3/33	15
Meropenem	4/33	20
Cefepime	3/33	15
Levofloxacin	2/33	10
Azithromycin	1/33	5
Cefixime	1/33	5
Ofloxacin	1/33	5
Total	20/33	100

Table 6. The outcome of UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae*

Isolate	Recovery	Death	Total
ESBL <i>E. coli</i>	18 (75%)	6 (25%)	24 (72.7%)
ESBL <i>K. pneumoniae</i>	8 (88.8%)	1 (24.2%)	9 (27.3%)
Total	26 (78.8%)	7 (21.2%)	33 (100%)

Meanwhile, those in 18-25 years category had the least UTIs with 5/63 which mainly caused by bacteria that did not produce ESBL (Table 3).

Empiric and Definitive Use of Antibiotics

Table 4 below shows that the empiric use of antibiotics therapy given to UTI patients were mostly ceftriaxone with a total of 27 patients (58.6%), which followed by cefoperazone, 6 patients (13.0%). Meanwhile, the other antibiotics such as levofloxacin and cefixime were each given to 2 patients (4.3%), and meropenem, ceftazidime, cefotaxime, ciprofloxacin, doxycycline, cotrimoxazole, metronidazole, ofloxacin, and vancomycin were each given to 1 patient (2.2%).

The use of antibiotics given to UTI patients due to *E. coli* and *K. pneumoniae* who are hospitalized at Dr Zainoel Abidin after the results of culture and antibiotic sensitivity test are available, which called definitive antibiotics, are shown in the table 5. The table informs that generally ceftriaxone is used with a total of 5 patients (25%). Meanwhile, other antibiotics therapy such as meropenem were administered to 4 patients (20%), levofloxacin to 2 patients (10%), cefoperazone and cefepime were each to 3 patients (15%). Azithromycin, cefixime and ofloxacin were each administered to 1 patient (5%). This shows that the results of culture and antibiotic sensitivity tests do

not change the administration of antibiotic therapy in UTI patients. This data indicates that there is bacterial resistance due to the use of inappropriate antibiotics like long duration of administration of antibiotics, too low or high dosage, and inaccurate initial diagnosis.

Outcome of UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae*

The occurrence of recovered patients from UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae* are 26 of 33 cases (78.8%), while the other 7 cases (21.2%) are reported died (Table 6).

DISCUSSION

Incidence rate of UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae*

Magliano et al (2012) reported that patients living in a city in North Italy showed the most common bacteria found in UTIs diagnosed patients was *E. coli* with a total of 9,344 (67.6%), followed by *K. pneumoniae* with a total of 1,217 (8.8%) from overall 12,549 Gram-negative isolates (90.8%).⁸ Endriani et al (2009) reported that the most common cause of UTIs were Gram-negative with 38 isolates (76%) from 50 isolates, most of them were *E. coli* and *K. pneumoniae*, 14 isolates (28%) and 13 isolates (25%) respectively. This was likely caused by bacteria-causing UTIs originated from normal flora of the gut or skin around the orificium urethra

entered the urinary tract.²

Research conducted by Hayati et al. (2017) showed that out of 48 *E. coli* isolates, 41 isolates (85%) had ESBL phenotypes, while out of 74 isolates of *K. pneumoniae*, 59 isolates (80%) had ESBL phenotype. This shows that out of a total of 122 isolates, 100 isolates had the ESBL phenotypes.⁷ This shows the high resistance of bacterial to antibiotics which can affect the recuperation of urinary tract infections.

Saharman et al. (2013) stated that the most common isolates of *Enterobacteriaceae* in the ICU ward of Cipto Mangunkusumo Hospital were *K. pneumoniae* with a total of 61 isolates (54.46%) which followed by *E. coli*, 15 isolates (13.39%) of all 112 *Enterobacteriaceae* isolates.⁹

The emergence of ESBL-producing bacteria poses a challenge in therapy, that the CLSI guidelines recommend reporting any ESBL-producing *E. coli* and *K. pneumoniae* isolates as bacteria that resistant to penicillins, third-generation cephalosporins, and aztreonam.⁵

Patient Characteristics by Gender

Sumolang et al (2013) also reported that women suffer from UTIs more frequently than men. UTIs caused by ESBL-producing *E. coli* were mostly occurring in female (48.5%) by comparison to male 24 to 16 cases, whereas UTIs caused by ESBL-producing *K. pneumoniae* is more common in male (18.2%) rather than female, respectively 6 and 9 cases.¹⁰

Diagnosis of UTIs is higher in women than in men due to several predisposing factors, such as the anatomical structure of the female urinary tract, which has a shorter urethra and is close to the anus which makes it easier for bacteria to enter the urinary tract. In postmenopausal women, the secretion of estrogen which acts as a barrier to vaginal colonization of *Enterobacteriaceae* has a significant reduction.¹⁰ The other study also showed that out of 57 patients, 40 patients (70.2%) were female while the other 17 patients (29.8%) were men.¹¹

Bacteria causing UTI could grow in the surface of the urethra both in men and women, however, periurethral in women provide more space since it is placed in the

vaginal cavity which anatomically possible for more bacteria to grow. Furthermore, women also have a shorter urethra than men that make bacteria can move easily from vagina to urethra, which increases the possibility of uropathogenesis into the bladder which allow it to multiply in the urine and invade the bladder wall or climb further up to the kidneys. Male patients usually develop UTI due to anatomical abnormalities, urinary tract stones, or urinary tract obstruction.^{11,12}

Patient Characteristics by Age

Many predisposing factors that lead to UTIs in older people including prostate hyperplasia in men and postmenopausal estrogen deficiency in women. Recurrence of UTIs in women due to decreasing production of estrogen which causes the pH of vaginal fluid to rise can also lead to increasing the microorganisms in the vagina.^{10,13}

Febrianto, et al (2013) reported that young women had a higher incidence of UTIs since it was triggered by hygiene, sexual intercourse, and the use of contraceptives or spermicide gels which could lead to the risk of UTIs by changing the normal flora in the vagina.¹¹

Empiric and Definitive Use of Antibiotics

Based on the research of Febrianto et al. (2013), antibiotics that were given to 83 UTIs patients who were hospitalized in 2012, at Undata Hospital, Palu, was ciprofloxacin with a distribution of 44 patients (52.4%) which followed by ceftriaxone of 31 patients (37.8%) and cefotaxime of 3 patients (3.7%).¹¹ Ciprofloxacin is the most common use as a treatment for UTI patients. Fluoroquinolone inhibits the DNA gyrase mechanism which produces during the growth and reproduction process of bacteria. Ciprofloxacin has a bactericidal effect in treating infections caused by *E. coli* and other Gram-negative bacteria.¹¹

Ceftriaxone is one of the cephalosporin class that is widely used as therapy in UTI patients. It is a broad-spectrum antibiotic that may treat both Gram-positive and Gram-negative bacteria. Intensive use of broad-spectrum cephalosporins such as ceftriaxone and cefoperazone have

triggered resistance to *Enterobacteriaceae* bacteria, resulting in the emergence of antibiotic-resistant strains of bacteria since the bacteria may produce ESBL enzyme.¹⁴ Kumala's research (2009) stated that the penicillins group was often used for UTI treatment initially, but nowadays many of them were resistant to it which lead to the usage of cephalosporins.¹⁵

ESBL is an enzyme that may cause resistance to almost all β -lactam antibiotics including penicillin, cephalosporins and monobactams. β -lactamase enzyme first discovered was called TEM-1, TEM was characterized by the presence of the serine amino acid on its active side. The mutation of one amino acid in TEM-1 results in the formation of a new enzyme called TEM-2. In every mutation, a new enzyme with different hydrolysis ability of the beta-lactam ring will be produced. TEM-3 in bacteria that produces β -lactamase is the first β -lactamase that was grouped in ESBL-producing bacteria in any TEM variants.¹⁴

The CLSI guidelines (2018) suggest the sensitivity of *Enterobacteriaceae* for group U (urine) using cephalothin as the first-line treatment, whereas this group of bacteria is resistant to it, lomefloxacin or ofloxacin or norfloxacin can be used. If this group is also resistant to it, the alternative drug is nitrofurantoin, and if sulfamethoxazole can not be provided, the last option is trimethoprim.¹⁶

Outcome of UTIs caused by ESBL-producing *E.coli* and *K. pneumoniae*

Inappropriate use of antibiotics does not provide an optimal antibacterial effect. This can cause harm to the patient, resulting in bacterial resistance leading to a longer length of stay and increasing treatment cost.¹⁴

Antibiotics should ideally be used to treat the infection once the organism has been identified and tested for sensitivity. UTI diagnosis is carried out by microbial examination of urine specimens to determine the species, sensitivity, and resistance pattern of microorganisms obtained.¹¹

The main cause of antibiotic resistance is its widespread and irrational use of antibiotics. Patients in hospital care receive antibiotics as treatment or prophylaxis.

According to Utami (2011), there is approximately 80% use of antibiotic which 40% are based on inaccurate aetiology, such as viral infection.¹⁷

Rational treatment is one way to prevent bacterial resistance to antibiotics which allow the accuracy of indication, the drug of choice, dosage, frequency, and duration of antibiotic usage. The rational antibiotics are chosen based on the results of the antibiotic sensitivity test, this is to avoid giving resistant antibiotics.¹⁴

CONCLUSION

In conclusion, about half of the *E. coli* and *K. pneumoniae* causing UTIs reported at Dr Zainoel Abidin's General Hospital were ESBL-producing *E. coli* and *K. pneumoniae*. This study shows that ESBL-producing *E. coli* are more common causing UTI rather than non-ESBL, whereas the most frequent cause from *K. pneumoniae* is the non-ESBL one. The study shows that the most commonly prescribed antibiotic therapy is ceftriaxone. UTIs caused by ESBL producing *E. coli* and *K. pneumoniae* generally occurs at the age of 56-64 years which women suffer from UTIs more frequently than men. Furthermore, the outcome of UTI caused by ESBL-producing *E. coli* and *K. pneumoniae* of this study shows poor results which find 21.2% of patients died.

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AUTHOR CONTRIBUTION

Zinatul Hayati shares the first authorship whom carried out the first concept and design of this study. As for main the content, clinical studies, and data analysis, Zinatul Hayati was helped by Kurnia F Jamil, Afrianda Azhari, Wilda Mahdani, and Teuku Fadrial Kamil. Afrianda Azhari performed the statistical analysis. During the discussion of this study, Zinatul Hayati also helped by Asyriya Yossadania, Dahril, and Yopie Afriandi Habibie. All of the contributors participated in searching for research material and helped to draft the manuscript.

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CONFLICT OF INTEREST

We have no potential conflicts of interest to report. All authors read and approved the final manuscripts.

ETHICAL CONSIDERATION

This research has received *ETHICAL APPROVAL* from Health Research Ethics Commission of Faculty of Medicine of Univesity of Syiah Kuala – Dr Zainoel Abidin Hospital (*KEPPKN Registration Number: 1171012P*) by number: *09/EA/FK/2018*

REFERENCES

- Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol.* 2015;13(5):269–84.
- Endriani R, Andriani F, Alfina D. Pola Resistensi Bakteri Penyebab Infeksi Saluran Kemih (ISK) Terhadap Antibakteri di Pekanbaru. *J Natur Indones.* 2010;12(2):130–5.
- Sutandhio S, Alisardjono L, Lusida MI. Distribusi dan Pola Kepekaan Enterobacteriaceae dari Spesimen Urin di RSUD Dr Soetomo Surabaya Periode Januari - Juni 2015. *Widya Med.* 2015;3(1):2–9.
- Cockerill FR. Performance Standards for Antimicrobial Susceptibility Testing. 21st ed. Vol. 31, Twenty-first Informational Supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
- Warganegara E, Apriliana E. The Determining type of Extended Spectrum Beta Lactamase Enzyme (ESBL) from *Escherichia coli* resistance Cephalosporine of third Generation in RSUD Abdoel Moeloek Bandar Lampung. *J Kedokt Univ Lampung.* 2014;4(7):87–96.
- Kuntaman K, Hadi U, Paraton H, Qibtiyah M, Wasito E, Koendhori E, et al. Surveilain multi senter *Klebsiella pneumoniae* and *Escherichia colipenghasil ESBL* di Indonesia. *Maj Kedokt Indones.* 2013;
- Hayati Z, Rizal S, Putri R. Isolation of Extended-Spectrum B-lactamase (ESBL) Producing *Escherichia coli* and *Klebsiella pneumoniae* from Clinical Isolates in RSUD dr . Zainoel Abidin , Aceh. *Int J Trop Vet Biomed Res.* 2019;4(5):16–22.
- Magliano E, Grazioli V, Deflorio L, Leuci AI, Mattina R, Romano P, et al. Gender and Age-Dependent Etiology of Community-Acquired Urinary Tract Infections. *Sci World J.* 2012;
- Saharman YR, Lestari DC. Phenotype Characterization of Beta-Lactamase Producing Enterobacteriaceae in the Intensive Care Unit (ICU) of Cipto Mangunkusumo Hospital in 2011. *Indones J Intern Med.* 2013;45:11–6.
- Sumolang SAC, Porotuo J, Soeliongan S. Pola Bakteri pada Penderita Infeksi Saluran Kemih di RSUD Prof. dr. R.D. Kandou Manado. *J e-Biomedik.* 2013;1(1):597–601.
- Febrianto AW, Mukaddas A, Faustine I. Rasionalitas Penggunaan Antibiotik pada Pasien Infeksi Saluran Kemih (ISK) di Instalasi Rawat Inap RSUD Undata Palu Tahun 2012. *Online J Nat Sci.* 2013;2(3):20–9.
- Lee JBL, Neild GH. Urinary Tract Infection. *Medicine (Baltimore).* 2007;35(8):423–8.
- Mantu FN, Goenawi LR, Bodhi W. Evaluasi Penggunaan Antibiotik pada Pasien Infeksi Saluran Kemih di Instalasi Rawat Inap RSUP. Prof. DR. R. D. Kandou Manado Periode Juli 2013 - Juni 2014. *Pharmacon J Ilm Farm.* 2015;4(4):196–202.
- Rachman NO, Prenggono MD, Budiarti LY. Uji Sensitivitas Bakteri Penyebab Infeksi Saluran Kemih pada Pasien Diabetes Melitus terhadap Seftriakson Levofloksasin dan Gentamisin. *Berk Kedokt.* 2016;12(2):205–13.
- Kumala S, Raisa N, Rahayu L, Kiranasari A. Uji Kepekaan Bakteri yang Diisolasi dari Urin Penderita Infeksi Saluran Kemih (ISK) terhadap Beberapa Antibiotik pada Periode Maret-Juni 2008. *Maj Ilmu Kefarmasian.* 2009;VI(2):45–55.
- Cockerill FR. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. 23rd ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
- Utami ER. Antibiotik Resistensi dan Rasionalitas Terapi. *El-Hayah.* 2011;1(4):191–8.



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