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

**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%).

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

| Bacterial Characteristic | Isolate | Male | Female | Total |
|--------------------------|---------|------|--------|-------|
| E. coli                  | ESBL    | 8 (24.2%) | 16 (48.5%) | 24 (38.1%) |
|                          | Non ESBL| 7 (30%) | 9 (23.3%) | 16 (25.4%) |
| K. pneumoniae            | 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 2. **Patient Characteristics by Age**

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

Table 3. **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 |
| Ciprofloxacine   | 1/33  | 2.2 |
| Doxycycline      | 1/33  | 2.2 |
| Kotrimoksazol    | 1/33  | 2.2 |
| Metronidazole    | 1/33  | 2.2 |
| Ofloxacine       | 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.
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, cefazolin, cefotaxime, cefproziloxin, 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 Hospital 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 were 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%).
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.

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. 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 (54.6%) which followed by E. coli, 15 isolates (13.39%) of all 112 Enterobacteriaceae isolates.

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.

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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.

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.

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.

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.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 penicillin 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 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 Asyrla 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 University of Syiah Kuala – Dr Zainoel Abidin Hospital (KEPPKN Registration Number: 1171012P) by number: 09/EA/FK/2018

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