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RESEARCH ARTICLE

Factors influencing infections caused by *Extended Spectrum Beta Lactamase* (ESBL) producing bacteria in patients with urinary tract infections at RSUD dr. R. Soetijono Blora

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ABSTRACT

Urinary tract infection (UTI) is a bacterial infection found in pediatric patients. The prevalence of infections due to *Extended Spectrum Beta Lactamase* (ESBL)-producing *Enterobacterales* is increasing worldwide. This study aims to identify and analyze the factors influencing ESBL producing bacterial infection in UTI patients at the hospital of RSUD dr. R. Soetijono, Blora in January-March 2023. The results of this *cross-sectional* study showed that 58 respondents with urine culture results found *Enterobacterales* pathogenic bacteria. Based on the ESBL enzyme-producing antibiotic test, it was found that there were 39 ESBL people (67.2%) and 19 people (32.8%) Non-ESBL. The study variables were appropriate age, gender, history of catheter insertion, history of stones or urinary tract surgery, and history of taking antibiotics in the last six months. Chi-square determines the degree of significance, but the risk is counted using risk (odds ratio, etc.). Bivariate logistic regression showed that a history of catheter insertion and a history of antibiotics use in the last six months were significant risk factors—prevalence of UTIs due to ESBL-producing *Enterobacterales* in RSUD dr. R. Soetijono Blora during the study period was high, and the prudent use of antibiotics, especially the third-generation cephalosporins as therapy, is needed for preventive strategies to reduce antibiotic resistance.

1. Introduction

Urinary tract infection (UTI) is a urinary tract infection accompanied by bacterial colonization in the urine (bacteriuria). The presence of bacteriuria, which indicates UTI, is the growth of pure bacterial growth of more than 100,000 Colony forming units (CFU/mL). Patients who experience bacteriuria are sometimes without clinical signs and symptoms (asymptomatic) or may be accompanied by clinical signs and symptoms (symptomatic) (Ritonga *et al.,* 2018). The most common causes of UTIs are bacteria from the order Enterobacterales, for example, *Escherichia coli, Klebsiella pneumoniae, and Enterococcus sp* (Raz *et al.,* 2002a) (Leung *et al.,* 2019).

Antibiotic options for the treatment of UTIs include β-lactam antibiotics, β-lactamase inhibitors, fluoroquinolones—and carbapenems—rationality of using antibiotics in patients with UTI. As the use of antibiotics to treat UTIs increases, the causative pathogens begin to develop resistance, rendering empirical therapy ineffective (Aboumarzouk, 2014). The bacteria that produce the ESBL enzyme are resistant to multiple antibiotics (Aboumarzouk, 2014) (Shakya *et al.,* 2017).

ESBL are a group of enzymes that can hydrolyze various β-lactam class antibiotics, including penicillins, cephalosporins (ceftazidime, ceftriaxone),

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and monobactam (aztreonam), but do not hydrolyze cefamycins (cefoxitin) (Biutifasari, 2018). Bacterial resistance to antibiotics, especially β-lactam-class antibiotics, continues to increase alarmingly. Antibiotics of the β-lactam-group can become resistant due to the production of β-lactamase enzymes and ESBL) enzymes. Most genes coding for β-lactamase and ESBL enzymes in bacteria are found in plasmids. Plasmids are very mobile, which makes it easy to transfer resistance genes to other bacteria. The incidence of infection by ESBL-producing bacteria is proven to be increasing worldwide (Winarto, 2009). In addition, studies have reported that ESBL enzyme-producing bacteria cause higher morbidity and mortality than non-ESBL bacteria (Dhillon & Clark, 2012).

According to RSUD Dr. R. Soetijono Blora's medical records, there were 214 UTI patients in 2020. In 2021, the population decreased to 176, and in 2022, it increased to 240. Due to the increase in patients with urinary tract infections, it is necessary to investigate their causes in greater depth. According to preliminary research data, the majority of patients at the hospital of RSUD dr. R. Soetijono, Blora use -Lactam antibiotics. The highest prevalence of sufferers occurs between the ages of 26-36 years with a prevalence of 29.4 percent, followed by the ages of 36-45 years with a prevalence of 23.6 percent, ages 46-55 years with a prevalence of 17.6 percent, the ages of 16-25 years with a prevalence of 14.7 percent, the ages of 56-65 years with a prevalence of 11.8 percent, and finally the ages of over 65 years with a prevalence of 2.9 percent. Previous research indicated that the average prevalence of UTI among women is very high. Based on data on the use of antibiotics as therapy in RSUD, dr. R. Soetijono Blora, in 2022, the use of β-lactam antibiotics is the most compared to other antibiotics, with as many as 18,841 visits. Meanwhile, other antibiotics used were Aminoglycosides for 1,485 visits, Antiamoeba for six visits, Antifungal for 177 visits, Antiherpes for 29 visits, Antiseptic for 101 visits, Anti-TB for 142 visits, Quinolones for 3,682 visits, and Macrolides for 433 visits. β-lactam antibiotics used include amoxicillin, ampicillin, cefuroxime, sultamicilin, ceftriaxone, cefadroxil, cefazolin, cefixime, cefoperazone sulbactam, cefotaxime, ceftriaxone.

Understanding resistance mechanisms, identifying new antibiotics, and developing strategies to slow the spread of resistant bacteria are the primary goals of antibiotic resistance research. Aging weakens the immune system, making individuals more susceptible to infection. In addition, older individuals may have a higher incidence of chronic conditions requiring antibiotic treatment, which can lead to a higher frequency and duration of antibiotic use, thereby potentially increasing the risk of antibiotic resistance (Hu *et al.,* 2018). Other studies have concluded that, in addition to age, resistance to β-lactam antibiotics in UTI patients is also influenced by gender, urinary tract surgery history, and UTI recurrence (Mantu KFK, 2015).

The rising incidence of UTIs in RSUD dr. R. Soetijono Blora may have been precipitated by a case of resistance to β-lactam antibiotics, which are the most commonly used antibiotics. Therefore, it is necessary to conduct a study at RSUD dr. R. Soetijono, Blora on the status of β-lactam antibiotic resistance and the factors that influence it in patients with UTI. This study aims to determine and analyze the factors that influence ESBL producing bacteria, including age, gender, history of catheter insertion, history of stones or urinary tract surgery, and history of antibiotic use in the last 6 months. in UTI patients at RSUD dr. R. Soetijono, Blora.

2. Materials and Methods

This cross-sectional study was conducted between February and May of 2023 at RSUD dr. R. Soetijono, Blora. All UTI patients taking β-lactam antibiotics who were registered at RSUD dr. R. Soetijono Blora in 2022 comprised the study population. All UTI patients with positive bacterial cultures who were treated and registered at Dr. Soetijono Blora Hospital in 2022 provided samples for this study. Dr. R. Soetijono Blora sampling method utilized a technique of consecutive sampling, which included all subjects who met the research criteria. Patients diagnosed with UTI receiving β β-lactam antibiotic therapy, clear and contactable addresses, patients willing to participate in the study, and positive bacterial cultures were the inclusion criteria for the study sample. In the meantime, the exclusion criteria were patient identification with an incomplete medical record and patient refusal to complete the questionnaire. During the study period, the urine culture results of 58 participants revealed the presence of pathogenic Enterobacterales bacteria. Through medical record data and the distribution of respondent questionnaires, risk factors were identified. The variables of the study were age, gender, history of catheter insertion, history of kidney stones or urinary tract surgery, and history of antibiotic use within the previous six months. Chi-square test was used for univariate and bivariate data analysis. The Diponegoro University Health Research Ethics Committee approved protocol number 86/EC/KKP-FK-UNDIP/III/2023 on an ethical level.

3. Results

Table 1 shows that woman are the most prevalent known risk factor. 33 individuals (56.9%) had a history

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of UTI recurrence, 31 individuals (53.4%) had a history of catheter insertion, 34 individuals (58.6%) had a history of stones or urinary tract surgery, 37 individuals (63.8%) had a history of using antibiotics in the last 6 months months, and 10 individuals (10%) had a history of diabetes mellitus (17.2%). Another risk factor in age is known to be the same for those aged > 40 and 40, namely 29 individuals (50 percent).

Table 1. Respondent Characteristics

Variable	n (%)
Gender	
• Man	25 (43.1%)
• Woman	33 (56.9%)
Age	
• > 40 Years	29 (50%)
• ≤ 40 Years	29 (50%)
Catheter insertion history	
• No	24 (34%)
• Yes	34 (58.6%)
History of stones or urinary tract surgery	
• No	21 (36.2%)
• Yes	37 (63.8%)
History of antibiotic use in the last six months	
• No	25 (43.1%)
• Yes	33 (56.9%)

3.1. The relationship between gender with ESBL enzyme-producing bacteria

The incidence of ESBL enzyme-producing bacteria is 72% higher in males than in females, as shown in Table 2. The chi-square test yielded a *p*-value of 0.697, which is greater than 0.05, indicating that there is no statistically significant relationship between the sex variable and the presence of ESBL-producing bacteria.

3.2. The relationship between age the incidence of ESBL enzyme-producing bacteria

The incidence of ESBL enzyme-producing bacteria is % percent between ages > 40 and 40 years old (Table 3). The analysis using the chi-square test with a confidence level of 95% and a p-value of 1,000 ((*p*>0.05), indicating that there is no statistically significant relationship between the age variable and the presence of ESBL-producing bacteria.

Table 2. Bivariate analysis of sex with the occurrence of ESBL enzyme-producing bacteria

Gender	ESBL Enzyme Producing Bacteria		Total	*p-value*	OR (95% CI)
	Non-ESBL	ESBL			
Man	7 (28.0%)	18 (72.0%)	25 (100%)	0697	0.681 (0.221-2.096)
Woman	12 (36.4%)	21 (63.6%)	33 (100%)		
Total	19 (32.8%)	39 (67.2%)			

Description: *= Significant 5% on the *Chi-Square Test (Continuity Correction)*

Table 3. Bivariate analysis of age with the incidence of ESBL enzyme-producing bacteria

Age	ESBL Enzyme Producing Bacteria		Total	*p-value*	OR (95% CI)
	Non-ESBL	ESBL			
> 40 Years	9 (31.0%)	20 (31.0%)	29 (100%)	1,000	0.855 (0.285-2.563)
≤ 40 Years	10 (34.5%)	19 (65.5%)	29 (100%)		
Total	19 (32.8%)	39 (67.2%)			

Description: *= Significant 5% on the *Chi-Square Test (Continuity Correction)*

Table 4. Results of bivariate analysis of the history of catheter insertion with the incidence of ESBL enzyme-producing bacteria

Catheter insertion history	ESBL Enzyme Producing Bacteria		Total	*p-value*	OR (95% CI)
	Non-ESBL	ESBL			
No	13 (54.2%)	11 (45.8%)	24 (100%)	0.008*	5,515 (1,674-18,175)
Yes	6 (17.6 %)	28 (82.4%)	34 (100%)		
Total	19 (32.8%)	39 (67.2%)			

Description: *= Significant 5% on the *Chi-Square Test (Continuity Correction)*

3.3. The relationship between between catheter history variables and ESBL enzyme producing bacteria

The incidence of ESBL enzyme-producing bacteria was 82.4% higher among respondents with a history of catheter insertion, compared to 45.8% among respondents without a history of catheter insertion (Table 4). The Chi-Square test with a confidence level of 95% yielded a p-value of 0.008 (p<0.05), indicating that there is a statistically significant relationship between the history of catheter placement and the incidence of ESBL enzyme-producing bacteria.

3.4. The relationship between history of stones or urinary tract surgery with the incidence of ESBL enzyme-producing bacteria

Table 5 shows the incidence of ESBL enzyme-producing bacteria in patients with a history of urinary tract stones/surgery was 70.3% higher than in patients without a history of urinary tract stones/ surgery (61.9%). The chi-square test yielded a p-value of 0.718 (p>0.05), indicating that there is no statistically significant relationship between the history of stones/ urinary tract surgery and the presence of ESBL-producing bacteria.

3.5. The relationship between history of antibiotic use in the last 6 months with the occurrence of ESBL enzyme-producing bacteria

The incidence of ESBL enzyme-producing bacteria in patients with a history of stones/urinary tract surgery is 70.3% higher than in patients without a history of stones/urinary tract surgery (61.9%). The chi-square test yielded a p-value of 0.718 (p>0.05), indicating that there is no statistically significant relationship between the history of stones/urinary tract surgery and the presence of ESBL-producing bacteria.

4. Discussion

The findings of this study are consistent with the previous research that found no association between gender and the incidence of multiresistant bacteria (p=0.171, OR=0.259, 95% CI, 0.050-1.3) (Sinatria L.R, 2019). Other studies have found no correlation between gender and the incidence of MDR (p-value = 0.13) (Magill *et al.,* 2014)). However, these findings contradict the research conducted, which indicates a correlation between male and female respondents and the incidence of MDR (p <0.0001) (Raz *et al.,* 2002b).

This study is consistent with previous research indicating that the incidence of multiresistant bacteria was highest in individuals under 40 years of age (p=0.637, OR=0.496, 95% CI: 0.496-4.898) (Sinatria, 2019). According to previous research, there is no correlation between age and the incidence of MDR (p-value = 0.36) (Anggraini *et al.,* 2020). However, these results are not in line with previous research, which showed that there is a relationship between age and the incidence of MDR (p <0.0001) (Raz *et al.,* 2002b).

This study contradicts previous findings that a history of urinary catheter use is not associated with the incidence of urinary tract infections caused by ESBL-producing bacteria (p = 0.679, OR 95% CI: 1.107 to 2.110). (0.684-1.793) (2017) (Harinda, 2022) In addition, other studies indicate that a history of catheter insertion within the past three months (p=0.392, OR=3.333, 95% CI: 0.359-30.948) is associated with an increased risk of death (Sinatria, 2019)).

Table 5. Results of bivariate analysis of the history of stones or urinary tract surgery with the incidence of ESBL enzyme-producing bacteria

History of stones or urinary tract surgery	ESBL Enzyme Producing Bacteria		Total	*p-value*	OR (95% CI)
	Non-ESBL	ESBL			
No	8 (38.1%)	13 (61.9%)	21 (100%)	0.718	1.445 (0.471-4.494)
Yes	11 (29.7%)	26 (70.3%)	37 (100%)		
Total	19 (32.8%)	39 (67.2%)			

Description: *= Significant 5% on the *Chi-Square Test (Continuity Correction)*

Table 6. Results of bivariate analysis of the history of antibiotic use in the last six months with the occurrence of ESBL enzyme-producing bacteria

History of antibiotic use in the last six months	ESBL Enzyme Producing Bacteria		Total	*p-value*	OR (95% CI)
	Non-ESBL	ESBL			
No	13 (50.2%)	12(48.0%)	25 (100%)	0.015*	4,875 (1,494-15,904
Yes	6 (18.2%)	27 (81.8%)	33 (100%)		
Total	19 (32.8%)	39 (67.2%)			

Description: *= Significant 5% on the *Chi-Square Test (Continuity Correction)*

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This finding contradicts a meta-analysis finding that a history of catheterization increases the risk of ESBL-caused UTIs by 3.3-fold. However, the duration of urinary catheterization was not mentioned in the study (Larramendy *et al.,* 2020). Prior research revealed that the use of a urinary catheter increased the risk of UTI due to EBSL by 2.36-fold (95 % CI: 1.15–4.98; *p* 0.05) (Goyal *et al.,* 2019). According to additional studies, the use of a urinary catheter is a significant risk factor for UTIs caused by E. coli ESBL (OR 3.02, 95% CI: 1.27-7.18, p 0.01) (Al-Jamei *et al.,* 2019). In addition, a value for the Odds Ratio (OR) of 5,515 (95% CI: 1,674-18,175) was determined. This indicates that respondents with a history of catheter insertion are 5,515 times more likely to have ESBL enzyme-producing bacteria than respondents without a catheter insertion history.

The use of various invasive medical devices is also linked to the occurrence of ESBL infections. The installation of medical devices such as peripheral venous catheter tubes, urinary catheters, and nasogastric tubes is typically performed by paramedics at the Hospital of Dr. R Soetijono Blora, where the likelihood of the equipment being sterile is extremely high. It is crucial to provide paramedics with the proper training and stricter operating standards for installing invasive medical devices, such as hand hygiene.

According to the study's findings, the incidence of ESBL enzyme-producing bacteria among respondents with a history of urinary tract stones or surgery was 70.3% higher than among respondents without a history of urinary tract stones/surgery (61.9%). According to these findings, there is no association between a history of urinary tract stones or urinary tract surgery and the incidence of MDR (*p*-value =0.0938) (Killgore *et al.,* 2004). However, these results contradict the research that indicates a correlation between respondents with a history of urinary tract stones or urinary tract surgery and the prevalence of MDR (*p*-value = 0.03) (Johnson *et al.,* 2008).

A history of urinary tract stones was found to be a significant risk factor for UTI caused by ESBL-producing bacteria (OR 3.00; $p = 0.03$) in a separate study involving patients older than 18 years (Koksal *et al.,* 2019). Another study involving an adult population with community UTIs infected with ESBL bacteria reached the same conclusion (Quan *et al.,* 2021). In a previous study involving patients with UTIs and urinary tract stones, cultures of urinary tract calculus stones and urine culture isolates were found to be multi-drug resistant when compared to bacteria (Shah *et al.,* 2020). In addition, an odds ratio (OR) of 1,445 (95 % CI: 0.471-4.494) was determined. This indicates that respondents with a history of urinary tract stones or urinary tract surgery are 1,445 times more likely to have ESBL enzyme-producing bacteria than respondents without a history of urinary tract stones or surgery.

This study revealed that the variable history of antibiotic use in the previous six months had a significant association with the occurrence of ESBL enzyme-producing bacteria, but was not the primary factor influencing the incidence of ESBL bacteria in UTI patients. This is consistent with the findings of previous studies, which indicate that antibiotic use within the previous three months is a significant risk factor for E. coli ESBL-associated UTI (OR 2.76, 95% CI: 1.11-6.98, *p* 0.02) (Al-Jamei *et al.,* 2019). The results of a study on pediatric patients at a hospital in Michigan indicated that antibiotic use in the previous three months was significant (OR 4.17, 95% CI: 1.85-9.09, *p* 0.01) (Hebert *et al.,* 2019).

It is also comparable to previous studies in which antibiotics were used within the previous six months (OR = 2.06; 95% CI, 1.78-2.02; *p* 0.005) (Flokas *et al.,* 2017). It is also comparable to previous studies in which antibiotics were used within the previous 6 months (OR = 2.06; 95% CI, 1.78-2.02; *p* 0.005). (P=1,000, OR=0.865, 95% CI, 0.210-3.565) (Sinatria, 2019). In addition, a value for the Odds Ratio (OR) of 4,875 (95 percent confidence interval: 1,494-15,905) was obtained. This indicates that respondents with a history of antibiotic use in the previous six months had 4,875 times the incidence of ESBL enzyme-producing bacteria compared to respondents with no history of antibiotic use.

5. Conclusions

Dr. R. Soetijono Blora's occurrence of ESBL enzyme-producing bacteria is associated with a variable history of catheter insertion and antibiotic use in the previous six months, according to the research findings.

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Conflict of interest

All authors have no conflict of interest in this article.

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