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Trends in antimicrobial resistance of extended-spectrum beta-lactamase-producing *Escherichia coli* in urinary tract infections in ICU and non-ICU settings at Ngoerah Hospital, 2020-2022

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ABSTRACT

Background: Urinary Tract Infection (UTI) is one of the most common nosocomial infections, with *Escherichia coli* (*E. coli*) as the primary pathogen. The misuse and overuse of antibiotics has led to the emergence of antibiotic resistance, particularly in Extended-Spectrum Beta-Lactamase (ESBL)-producing *E. coli*. This resistance presents a significant challenge in managing UTIs, especially among ICU and non-ICU ward patients. This study aims to analyze trends in antibiotic resistance of ESBL-producing *E. coli* in UTI patients in ICU and non-ICU settings at Ngoerah Hospital during 2020–2022.

Methods: A descriptive study with a cross-sectional approach was conducted. The inclusion criteria of this study were samples with identification results of *E. coli* bacteria with VITEK 2 Compact (bioMérieux, France), which showed *E. coli* with a probability greater than or equal to 90% and accompanied by sensitivity of *E. coli* bacteria to antibiotics.

Result: Among 789 samples meeting inclusion criteria, 90% (714) were from non-ICU wards, while 10% (75) were from ICU wards. ESBL-producing *E. coli* accounted for 53% (416), while non-ESBL strains constituted 47% (373). The prevalence of ESBL-producing *E. coli* in non-ICU wards increased from 43% (96 isolates) in 2020 to 47% (129 isolates) in 2021 and 51% (149 isolates) in 2022. In ICU wards, prevalence rose from 3% (6 isolates) in 2020 to 4% (12 isolates) in 2021 and 8% (24 isolates) in 2022. Tigecycline, meropenem, and ertapenem demonstrated high sensitivity (≥96%), while beta-lactam antibiotics like ampicillin, cefixime, and cefazolin showed 100% resistance.

Conclusion: The increasing resistance of ESBL-producing *E. coli*, particularly in non-ICU settings, highlights the need for strict antibiotic policies and monitoring to prevent further resistance.

Keywords: Urinary Tract Infection, *Escherichia coli*, ESBL, Antibiotic Resistance, ICU, Non-ICU.
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INTRODUCTION

Urinary tract infection (UTI) is an inflammatory process caused by microorganisms that multiply in the urinary tract. This disease can be found in all ages, but is more common in women than in men because the distance between the urethra and rectum is greater in men than in women. In addition, the bactericidal component of the prostate can reduce the risk of men getting urinary tract infections.[1] Currently, UTIs rank second when sorted after respiratory tract infections, with a total of 8.3 million per year. Risk factors for UTI are age, gender, treatment room, use of catheters, administration of antibiotics, length of treatment, and bacteria, which are the most important.[2] The most common bacteria found in urinary tract infections are *E. coli*.[3] *E. coli* is a gram-negative bacterium that belongs to the Enterobacteriaceae family. These bacteria have virulence factors that can cause infections due to increased colonies and invasion.[4,5] Suppose *E. coli*, which was initially within normal limits, gets additional virulence genes from other microorganisms through gene transfer mechanisms (transformation), plasmid transfer (conjugation), or gene transfer through bacteriophages (transduction). In that case, the bacteria can turn into pathogens, and the diseases caused can vary.[6]

To control the number of diseases and even prevent deaths caused by infectious diseases, one of which is UTIs, antibiotics (antimicrobials) are used. In this case, antibiotics commonly used for treating UTI are cotrimoxazole, fluoroquinolone, beta-lactam groups such as penicillin, and cephalosporin.[5] After several studies, it was found that the use of antibiotics for UTIs was no longer effective due to the emergence of bacterial resistance caused by changes in resistance patterns that were faster than other infections and the discovery of bacteria producing extended-spectrum beta-lactamase (ESBL).[7] Extended-spectrum beta-lactamase is an enzyme with the ability to hydrolyze beta-lactam antibiotics, causing resistance to these types of

antibiotics. The resulting resistance is quite broad, encompassing various classes of antibiotics, including penicillin, broad-spectrum cephalosporins of generations 1, 2, and 3 (such as ceftazidime, cefotaxime, and ceftriaxone), monobactams (like aztreonam), aminoglycosides, trimethoprim-sulfamethoxazole, and fluoroquinolones. However, certain groups remain unaffected, specifically the carbapenems (including imipenem, meropenem, and ertapenem)[7,8] Based on the background description above, the purpose of this study was to determine the trend of resistance of ESBL-producing *E. coli* bacteria to antibiotics in UTI patients at Ngoerah Hospital so that it can determine the empirical therapy given in the future.

METHODS

This study is a retrospective descriptive study with a cross-sectional approach. This study was conducted at the Clinical Microbiology Installation of Ngoerah Hospital from January to June 2024. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Udayana University with protocol number 0478/UN14.2.2.VII.14/LT/2024.

The sample of this study was secondary data, namely the result of *E. coli* identification using VITEK 2 Compact (bioMérieux, France) at the Clinical Microbiology Installation of Ngoerah Hospital in 2020-2022, which were obtained using a total sampling method. This study includes all identification results that had a probability greater than or equal to 90% and were accompanied by the sensitivity of *E. coli* to antibiotics. The excluded samples were those in which the bacteria's sensitivity was terminated to minimize selection bias. The differentiation between ICU and non-ICU patients was based on hospital records, ensuring accurate categorization. The collected data were processed using Microsoft Excel, and univariate analysis was performed to describe the variables of the study, i.e., the resistance pattern of *E. coli* to antibiotics and the patient wards.

RESULTS

Based on the inclusion and exclusion criteria of this study, 789 samples are included out of 1,910 samples. According to Table 1, the samples consisted of 546 females (69%) and 243 males (31%). Based on the age distribution, most samples are in the 46-65 year age group (n = 344, 43%), followed by the over 60-year age group (n = 210, 27%). This shows that this study was dominated by the elderly adult group. The samples were obtained from non-ICU (n = 714, 90%) and ICU (n = 75, 10%). According to the phenotype of the *E. coli*, 416 samples were infected by ESBL-producing *E. coli* (53%), which shows that there was resistance to beta-lactam antibiotics. Among them, 374 isolates (90%) were obtained from non-ICU and 42 isolates from ICU (10%).

According to Figure 1, the prevalence rate significantly increased from 24% (102 isolates) in 2020 to 34% (141 isolates) in 2021 and reached 42% (173 isolates) in 2022. This reflects that antibiotic resistance has become a serious problem, especially in the beta-lactam group.

Bacterial culture and sensitivity tests using VITEX-2 Compact (bioMérieux) were performed, and the results are presented in Figure 2. In the ICU in 2020, there were only 6 isolates (3%) of ESBL-producing *E. coli* and 9 isolates (4%) of non-ESBL *E. coli*. Meanwhile, UTIs due to ESBL-producing and non-ESBL *E. coli* in non-ICU were higher, with 96 isolates

Table 1. Characteristics of samples

	Total (n=789)	Percentages (%)
Sex		
Male	243	31.0
Female	546	69.0
Age (years)		
< 5	47	6.0
5-11	24	3.0
12-25	47	6.0
26-45	117	15.0
46-65	344	43.0
> 65	210	27.0
Ward		
ICU	75	10.0
Non-ICU	714	90.0
ESBL Phenotype		
ESBL-producing *E. coli*	416	53.0
Non-ESBL *E. coli*	373	47.0

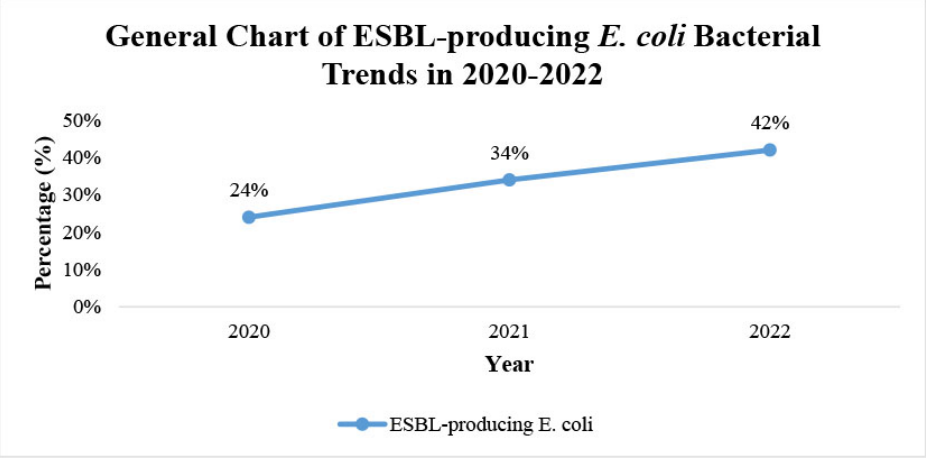

Figure 1. General chart of ESBL-producing *E. coli* bacterial trends in 2020-2022.

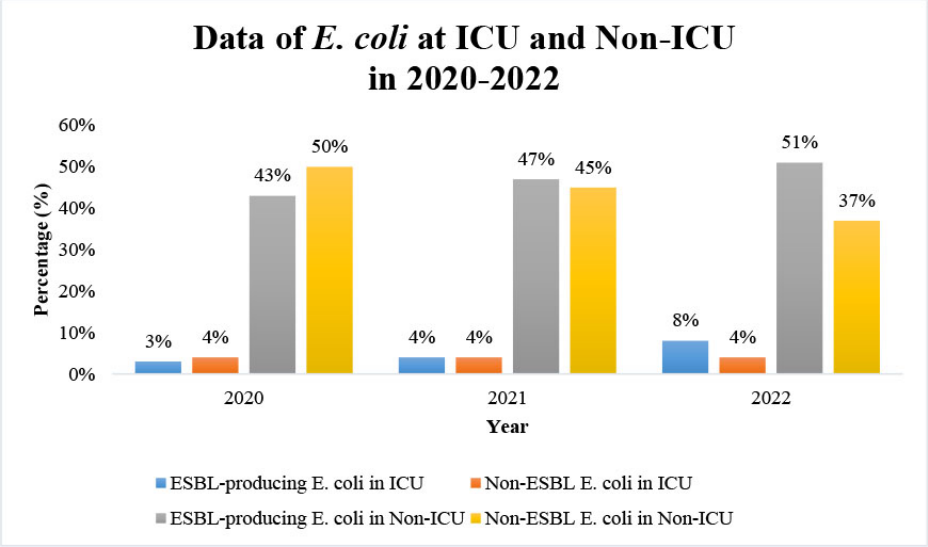

Figure 2. Data on *E. coli* in the ICU and non-ICU in 2020-2022.

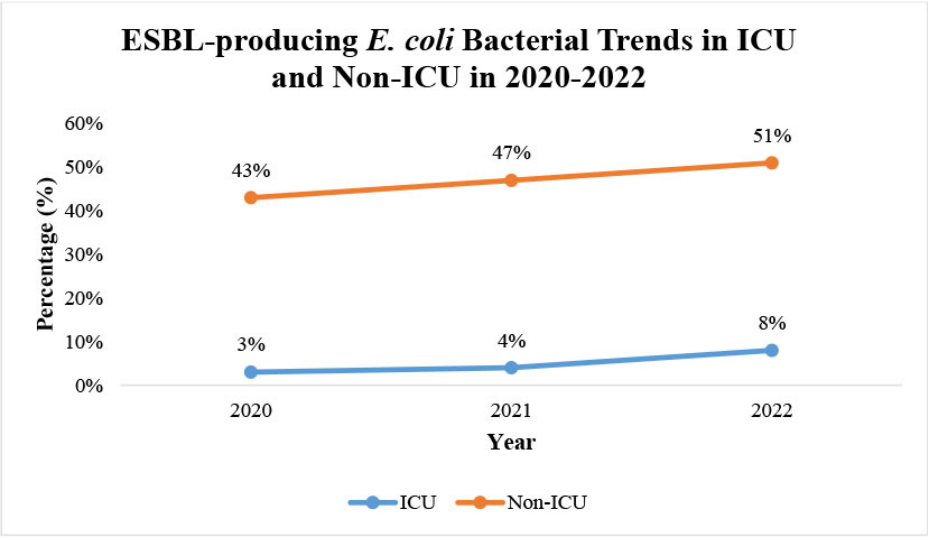

Figure 3. ESBL-producing *E. coli* bacterial trends in ICU and non-ICU in 2020-2022.

(43%) and 110 isolates (50%). These data show that UTIs due to ESBL-producing *E. coli* in non-ICU were higher than in ICU in 2020.

In 2021, there was an increase in UTI cases due to *E. coli* in non-ICU compared to the previous year, which consisted of 129 isolates of ESBL-producing *E. coli* (47%) and 123 isolates of non-ESBL *E. coli* (45%). Meanwhile, in the ICU, UTI cases slightly increased to 12 isolates (4%), both ESBL-producing and non-ESBL *E. coli*. These trends indicate that UTIs due to ESBL-producing *E. coli* in non-ICU settings keep growing, while in the ICU, they are relatively more controlled.

In the following year, 2022, the amount of *E. coli* in the ICU was significantly increased to 24 isolates of ESBL-producing *E. coli* (8%) and 12 isolates of non-ESBL *E. coli* (3%). On the other hand, the isolates of ESBL-producing *E. coli* in non-ICU were also increased to 149 (51%), but the isolates of non-ESBL *E. coli* were decreased to 107 (37%). These trends show that ESBL-producing *E. coli* increased, both in ICU and non-ICU, with a more significant spike in non-ICU.

Overall, it was found that the percentage of ESBL-producing *E. coli* in the ICU increased every year, although in small amounts. Meanwhile, for non-ESBL *E. coli* in the ICU, a stable trend was found every year at 4% (Figure 3). On the other hand, in the non-ICU, a significant increase was found related to ESBL-producing *E. coli*, while non-ESBL *E. coli* experienced a gradual decline.

Figure 3 shows the trend of ESBL-producing *E. coli* infections in ICU and non-ICU wards from 2020 to 2022. From the figure, there is a consistent and significant increase in percentage in both ICU and non-ICU every year. In non-ICU patients, the prevalence of ESBL-producing *E. coli* has consistently increased from year to year. In 2020, the prevalence was recorded at 43%, then increased to 47% in 2021, and reached 51% in 2022. This trend shows that non-ICU patients, although not in critical condition like in the ICU, still have a high risk of ESBL-producing *E. coli* infection. This could be due to several factors, such as the use of broad-spectrum antibiotics, care in long-term care facilities, and a history of repeated hospitalizations. In ICU patients, the prevalence is lower than in non-ICU patients but also shows a gradual increase. In 2020, only 3% of ESBL-producing *E. coli* isolates were found in ICU patients. This prevalence increased to 4% in 2021 and rose to 8% in 2022. Although the increase was not as high as in the non-ICU group, the risk of infection in ICU patients still needs to be watched out for.

Figure 4 shows the results of the sensitivity test of several antibiotics against ESBL-producing *E. coli* bacteria carried out using the VITEX-2 Compact test (bioMérieux) from 2020 to 2022. The antibiotics used in this study include several groups, such as the Monobactam and carbapenem groups, the aminoglycoside, fluoroquinolone, tetracycline, nitrofuran groups, and a combination of sulfonamide and trimethoprim. In the figure above, the sensitivity of each antibiotic is shown in percentage form for three consecutive years (2020, 2021, 2022), which are marked in blue, orange, and gray. The recommended sensitivity limit is 80%; antibiotics above this threshold are optimal for use as empirical therapy.

In 2020, it was found that the antibiotics ertapenem, meropenem, and tigecycline had very high sensitivity with a value of 100%, indicating their effectiveness as the primary treatment option for ESBL-producing *E. coli* infections in UTI patients. Then, followed by amikacin (99%), nitrofurantoin (96%), and piperacillin-

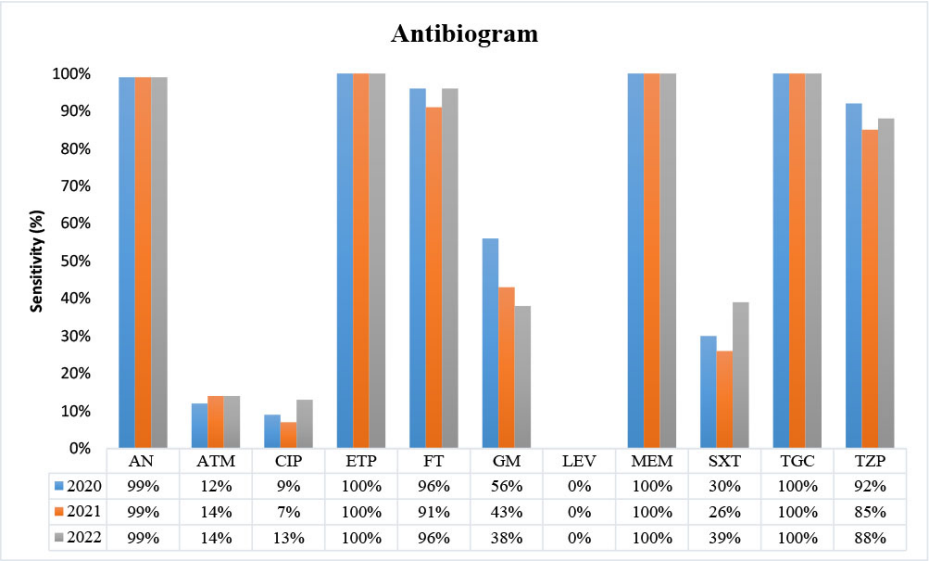

Figure 4. Sensitivity pattern of ESBL-producing *E. coli* to antibiotics. *Note: AN (Amikacin), ATM (Aztreonam), CIP (Ciprofloxacin), ETP (Ertapenem), FT (Nitrofurantoin), GM (Gentamicin), LEV (Levofloxacin), MEM (Meropenem), SXT (Trimethoprim/Sulfamethoxazole), TGC (Tigecycline), TZP (Piperacillin/Tazobactam).*

tazobactam (92%), which showed a percentage above 80% as the optimal threshold for the use of these antibiotics as empirical therapy. Several other antibiotics were also found with percentages below 80%, namely gentamicin (56%), trimethoprim-sulfamethoxazole (30%), aztreonam (12%), and levofloxacin (0%), which indicated that these antibiotics were less effective for use as empirical therapy for UTI.

In 2021, the sensitivity trend of most antibiotics remained consistent from the previous year. Several antibiotics still showed high sensitivity, such as ertapenem, meropenem, and tigecycline, with a figure of 100% followed by amikacin at 99%, indicating that these antibiotics were able to kill ESBL-producing *E. coli* bacteria. Meanwhile, aztreonam (14%) experienced a slight increase in sensitivity compared to the previous year but could not be said to be effective because the percentage shown was still below the optimal threshold. Several antibiotics that experienced a slight decrease in sensitivity this year, namely nitrofurantoin (91%), piperacillin-tazobactam (85%), gentamicin (43%), trimethoprim-sulfamethoxazole (26%), and ciprofloxacin (7%).

In 2022, the trend in antibiotic sensitivity to ESBL-producing *E. coli* still showed a consistent pattern as in previous years, where several antibiotics continued to show high effectiveness. Antibiotics such as ertapenem, meropenem, and tigecycline still show 100% sensitivity, followed by amikacin at 99%. Furthermore, there are antibiotics such as nitrofurantoin (96%) and piperacillin-tazobactam (88%) which show a stable sensitivity pattern by remaining above the optimal threshold (80%), indicating that they are effective as empiric therapy options for UTI. On the other hand, trimethoprim-sulfamethoxazole (39%), gentamicin (38%), aztreonam (14%), ciprofloxacin (13%), and levofloxacin (0%) still have very low sensitivity levels, which are below the optimal threshold indicating that these antibiotics are not effective for use in UTI patients.

DISCUSSION

The results of the study showed that of the 789 urine samples identified as positive for *E. coli* bacteria categorized based on their characteristics, most samples consisted of females, with a total of 546 people (69%). The results of this study are in line with research conducted by Wijaya et al., namely that UTIs are much more common in females than in males.[9] In addition, in a study by Abalkhail et al., in Saudi Arabia, it was also found that females are more susceptible to urinary tract infections than males because anatomically females have a shorter urethra and its position is closer to the rectum, making it easier for *E. coli* bacteria to invade.[10]

In terms of age distribution, the results of the study showed that most patients were aged 46-65 years, with a total of 344 people (43%). Individuals aged 46-65 years, both females and males, are more likely to experience UTIs due to a combination of several factors, such as anatomy, hormones, and health. As males age, they often experience urinary retention due to anatomical changes or conditions such as benign prostatic hyperplasia that need to be watched out for. While in females, they will experience hormonal changes related to menopause such as decreased estrogen levels, which can cause changes in vaginal flora and increase susceptibility to infection. In addition, the prevalence of comorbidities such as diabetes and urinary incontinence rises with age, which further increases the risk of UTI.[11,12] This finding is in line with research conducted by Wijaya et al., which found the same results that UTI was dominated by the 46-65 year age group and this was reinforced by research in China by Jia et al., that the elderly adult age group is more susceptible to UTI.[9,13]

Furthermore, from 789 urine samples that met the inclusion criteria, it was found that the majority of samples came from patients treated in the non-ICU, with a total of 714 people (90%). In contrast, only 75 patients (10%) were treated in the ICU of Ngoerah Hospital in the period 2020 to 2022. This indicates that most of the patients in this study were UTI patients who did not require intensive care, or that severe UTI cases are rare and can be treated with non-intensive care, in a study conducted by Mahdani et al., at the dr. Zainoel Abidin Regional General Hospital in 2022 to 2023, the same results were also found, that the majority of urine samples containing ESBL-producing *E. coli* bacteria came from non-ICU.[14] This may occur due to several risk factors such as extended hospitalization, extensive antibiotic exposure, use of catheters, and supervision and prevention strategies in non-ICU rooms are not as strict as in the ICU.[14,15]

Regarding the phenotype of *E. coli* bacteria, 53% (416 isolates) were declared

ESBL-producing *E. coli*, indicating resistance to beta-lactam antibiotics. Meanwhile, 47% (373 isolates) were declared non-ESBL *E. coli*. However, in another study conducted by Siriphap et al., different results were found that of the total 11,065 *E. coli* isolates, only 4,706 isolates (42.5%) were ESBL-producing *E. coli*.[16] The same incident was also seen by Abalkhail et al. (2022), in which more non-ESBL *E. coli* bacteria (1,013 isolates) were found compared to ESBL-producing *E. coli* (510 isolates). The difference in results may occur due to differences in the methods used, namely, the two studies above used the Kirby-Bauer Disk Diffusion Test. Meanwhile, this study used the VITEK 2 Compact (bioMérieux) test method, which resulted in differences in interpretation and validation when identifying samples.[10]

The increasing trend in the incidence of ESBL-producing *E. coli* in ICU and non-ICU can be attributed to several factors, one of which is the use of broad-spectrum antibiotics that can trigger the emergence of resistant strains. Another contributing factor is the demographic characteristics of the patients. Older people with comorbidities such as diabetes or the use of urinary catheters are at increased risk for developing UTIs caused by ESBL-producing *E. coli* bacteria. The use of urinary catheters, which is common in both of these wards, will make it easier for *E. coli* bacteria to colonize and increase the likelihood of urinary tract infections in patients.[15,17]

This study found that urine samples from UTI patients identified and tested using VITEK 2 Compact (bioMérieux) showed significant resistance patterns to several antibiotics. The highest sensitivity was found in ertapenem, meropenem, and tigecycline antibiotics, with a sensitivity level of 100%. Other antibiotics that also showed high sensitivity levels were amikacin with 99%, nitrofurantoin with a value of 91%-96%, and piperacillin/tazobactam at 85%-92% for 3 years. All of these antibiotics-maintained sensitivity values above the optimal threshold of 80%, so they were still effective for primary treatment. On the other hand, several antibiotics still showed sensitivity levels below the optimal threshold, including aztreonam, ciprofloxacin, gentamicin, and levofloxacin. This study's results align with several other studies that also found similar results that *E. coli* had high resistance to beta-lactam antibiotics and other antibiotics.

The same results were found in a sensitivity test study conducted at the Clinical Pathology Laboratory of Ulin Hospital, Banjarmasin, from 2016 to 2018, it was found that the most sensitive antibiotics were the carbapenem (ertapenem, meropenem), tetracycline (tigecycline), and aminoglycoside (amikacin) groups with a sensitivity of 100%. However, several antibiotics that have a high level of resistance, namely ampicillin, aztreonam, cefazolin, cefepime, ceftazidime, and ceftriaxone, with a sensitivity of 0%.[18] Furthermore, a study was conducted at the Microbiology Laboratory of King Fahd Medical City (KFMC), Riyadh, Saudi Arabia, from 2019 to 2020. This study found consistent results, namely antibiotics with relatively high resistance values, namely the penicillin group (ampicillin) of 100%, third-generation cephalosporins (ceftriaxone and ceftazidime) of 99.61% and 98.43%, fourth (cefepime) of 97.45%, monobactam (aztreonam) of 99.22%, sulfonamide (trimethoprim-sulfamethoxazole) of 63.13% and fluoroquinolones (ciprofloxacin and levofloxacin) of 68.03% and 64.5%. Then, the most sensitive antibiotic was ertapenem at 100%, followed by meropenem and amikacin at 99.61%.[10]

On the other hand, quite different results were found in a study conducted at Zainoel Abidin General Hospital in Banda Aceh from January 2022 to July 2023. The study found that antibiotics with the highest sensitivity were the carbapenem group (doripenem, imipenem, meropenem) and the lipopeptide group (polymyxin B), with a percentage of 27.4%. However, this figure is below the optimal threshold compared to the studies mentioned above, so further research is needed regarding the sensitivity pattern at the hospital.[14]

Therefore, to minimize the high prevalence of resistance of ESBL-producing *Escherichia coli,* a multifaceted intervention strategy should be implemented, integrating antimicrobial stewardship programs (ASP), strict infection control measures, and continuous surveillance. Surveillance programs should continuously monitor resistance trends and guide empirical therapy adjustments. The use of diagnostic stewardship, such as rapid molecular testing, can ensure precise antibiotic selection and reduce unnecessary exposure. Additionally, de-escalation strategies, minimizing prolonged antibiotic use, and enhancing physician and patient education on antimicrobial resistance are crucial. Policies such as catheter-associated urinary tract infection (CAUTI) prevention bundles should be reinforced to reduce infection risk in hospitalized patients. Finally, integrating regional and global data on resistance patterns with local surveillance can provide a more comprehensive strategy to combat multidrug-resistant *E. coli*.

CONCLUSION

This study found that UTIs were dominated by female patients, aged 46-65 years, in the non-ICU, and ESBL-producing E. coli bacteria caused most UTI cases. The trend in the prevalence of ESBL-producing *E. coli* bacteria in both the ICU and non-ICU showed a significant increase every year from 2020-2022, with higher numbers in the non-ICU room. ESBL-producing E. coli bacteria isolated from urine specimens from the ICU and non-ICU at Ngoerah Hospital, 2020-2022, are sensitive to several antibiotics such as ertapenem, meropenem, tigecycline, amikacin, nitrofurantoin, and piperacillin-tazobactam, which have an effectiveness rate above 80%. Therefore, these antibiotics are effective as primary treatment.

CONFLICT OF INTEREST

There are no conflicts of interest regarding the manuscript.

ETHICS CONSIDERATION

This study was approved by the Research Ethics Commission of the Faculty of Medicine, Udayana University with protocol number 0478/UN14.2.2.VII.14/LT/2024.

FUNDING

None.

AUTHOR CONTRIBUTION

BS was responsible for the conceptualization and design of the study. The definition of intellectual content was provided collaboratively by BS, NNSB, and NNDF. Literature searches, clinical studies, experimental procedures, and data acquisition were conducted jointly by BS, NNSB, and NNDF. BS, NNSB, NNDF, and IPBM carried out the data and statistical analyses. The initial manuscript was prepared and edited by BS and NNSB, with all authors, including NNDF, participating in the review of the manuscript. BS and NNSB served as the guarantors of the study. All authors have read and approved the final version of the manuscript.

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