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Cross-resistance to antibiotics of *Escherichia coli* in the inpatient installation of general regional hospital "X" Bali, Indonesia

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ABSTRACT

Escherichia coli (*E. coli*) is a critical-priority group of Multidrug-resistant (MDR) bacteria and its spread can occur in hospital inpatient settings. Several studies showed that antibiotics consumption for inpatients can cause *E. coli* resistance to other antibiotics called cross-resistance. The aim of this study to determine the cross-resistance in *E. coli* to antibiotics in the inpatient installation of the regional general hospital "X" in Bali, Indonesia.This study was a non-experimental ecological study that utilized retrospective data from the inpatient installation databases at general hospital "X" in Bali, Indonesia. The independent variable is the antibiotics consumption defined as defined daily doses/100 bed-days and the dependent variable is the percentage of *E. coli* resistance during 2017-2020. To examine the presence of cross-resistance in *E. coli*, an analysis of the correlation between antibiotic usage and the percentage of *E. coli* resistance to different antibiotics will be performed. The Pearson correlation tests were used to analyze the correlation between the level of antibiotic consumption and the percentage of E. coli resistance to antibiotics. The results indicated a significant correlation between tetracycline consumption and increased resistance of *E. coli* to both meropenem and piperacillin-tazobactam ($r=0.8\text{-}1.0$; $p<0.05$). This showed that there is cross-resistance in *E. coli*. Tetracycline significantly correlates with increased E. coli resistance to meropenem and piperacillin-tazobactam. This suggests that the level of use of one antibiotic can influence *E. coli*'s resistance to other antibiotics.

Keywords: Defined Daily Dose (DDD), *Escherichia coli* (*E. coli*), gene transfer, selection pressure

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INTRODUCTION

Antibiotic resistance is currently one of the main problems in the health sector. Health service facilities, such as hospitals, are the main contributors to the development and cause of bacterial resistance (Laborda et al., 2022). Antibiotic resistance can cause various problems, both in health and economic sectors, such as treatment failure, healthcare-associated infections, and increased health costs. Therefore, bacterial resistance to antibiotics is called nightmare bacteria by the World Health Organization because it can threaten people's lives worldwide (Meriyani et al., 2023).

In 2017, the World Health Organization (WHO) published a list of the twelve most dangerous bacteria for human health, categorizing them into three primary groups: critical, high-priority, and medium-priority. Among these, critical bacteria have developed resistance to multiple antibiotics, necessitating the discovery of new treatments. One such critical bacterium is *Escherichia coli* (*E. coli*), which belongs to the *Enterobacteriaceae* family. *E. coli* exhibits resistance to various classes of antibiotics and can cause severe infectious diseases, including sepsis and pneumonia. Additionally, it is responsible for numerous nosocomial infections (Mancuso et al., 2021).

Hospital inpatient installation contributes to bacterial resistance to antibiotics, such as *E. coli* (Dirga et al., 2021). Previous studies showed that antibiotics for inpatients can cause bacterial resistance to other antibiotics, known as cross-resistance. The study conducted by Sedláková *et al* (2014) concluded that using piperacillin-tazobactam significantly causes *E. coli* bacteria to be resistant to ceftazidime. Another study in one of the Peru hospitals showed that ceftazidime can increase *Enterobacter spp*. resistance to piperacillin/tazobactam and ciprofloxacin (Pérez-Lazo et al., 2021). A study conducted in a Malaysian hospital indicated that increased usage of polymyxins could lead to carbapenem resistance in *Enterobacteriaceae* bacteria (Tan et al., 2022). These differences are caused by differences in individual genetic or ethnicity, environment, level of antibiotics, socioeconomic factors, such as public hygiene and food, and differences in infection control in each hospital (Mancuso et al., 2021; Tao et al., 2017; Vikesland et al., 2019).

A study to determine the cross-resistance of *E. coli* to antibiotics has not yet been conducted in Indonesia. This is important to increase awareness and rationality in choosing antibiotics. Therefore, this study aims to determine the cross-resistance of *E. coli* to antibiotics in the inpatient installation at general hospital "X" in Bali, Indonesia. Data on antibiotic cross-resistance, especially in *E. coli*, can help develop a rational antibiotic consumption program.

METHOD

Methods

This study was a non-experimental ecological investigation utilizing data from general hospital "X" in Bali, Indonesia. The data covered a four-year period from January 1, 2017, to December 31, 2020. This tertiary care hospital has a capacity of 300 beds. The bed occupancy rates (BOR) during this period were 42% in 2017, 50% in 2018, 59% in 2019, and 72% in 2020. Ethical clearance for this research was granted by the hospital in February 2021, with the approval number 15/PEPK/II/2021.

An ecological study is a correlational study that involves investigating the relationship between an exposure and an outcome across entire populations or groups (Aggarwal & Ranganathan, 2019). This study observes the effect of antibiotic use on the occurrence of cross-resistance in *E. coli*. In other words, this study examines the relationship between antibiotic use and *E. coli* resistance to other antibiotics. The independent variable of this study was the use of antibiotics expressed in a Defined Daily Dose (DDD) per 100 days of treatment. The dependent variable in this study was the percentage of *E. coli* resistance to antibiotics. The research utilized secondary data, which included information on antibiotic use, bed occupancy rate (BOR), the number of hospital beds from the Hospital Pharmacy Installation, and the antibiogram data, covering the period from 2017 to 2020.

Data Collection

Data collection for this study was conducted retrospectively. The required data included systemic antibiotic use from 2017 to 2020, the number of beds, and BOR obtained from the Hospital Information System. *E. coli* bacterial resistance data was obtained from bacterial culture results available in antibiograms. Antibiograms were obtained from the Prevention and Control of Antimicrobial Resistance in Hospital. This study used a total sampling method. The antibiotics were antibiotic systemic and based on the WHO's J01 Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification. The study's objective did not involve identifying genetic mutations responsible for antibiotic resistance; therefore, molecular techniques such as PCR and DNA sequencing were not utilized.

Data evaluation

This study observes the correlation between antibiotic usage and cross-resistance in *E. coli*. Initially, data on the level of antibiotic consumption and the percentage of antibiotic resistance is calculated. Descriptive analysis will be conducted to assess the completeness and suitability of the data. Complete data on antibiotic usage and the percentage of bacterial resistance for each year will be used for correlation analysis. To examine the presence of cross-resistance in *E. coli*, the correlation between antibiotic usage and the percentage of *E. coli* resistance to different antibiotics will be analyzed.

Data Analysis

Antibiotic consumption

The total number of systemic antibiotics used in this study was calculated using Microsoft Excel software and is expressed in defined daily doses (DDD) per 100 days of treatment. DDD per 100 days of treatment was calculated by multiplying the total number of systemic antibiotics sold with the total number of systemic antibiotics content sold during one year (g) per DDD WHO standard multiplied by the population, then multiplied by 365 days. The population was obtained by multiplying the number of beds in the hospital by the bed occupancy rate (BOR) (Rahmawati et al., 2019). The level of antibiotic use expressed in DDD per 100 days of treatment was then added up according to the antibiotics class.

Microbial resistance data

Data on antibiogram in 2017-2020 were used to calculate the percentage of *E. coli* resistance to antibiotics. Antibiogram data are obtained from the Prevention and Control of Antimicrobial Resistance in hospital, which provides data on culture tests and bacterial sensitivity testing to antibiotics. In this study, *E. coli* in the susceptible category (<30%), intermediate category (30%-60%) and resistant (>60%) to antibiotics. The percentage of *E. coli* resistance to antibiotics is calculated by dividing the number of *E. coli* isolates that are resistant to antibiotics by the total number of *E. coli* isolates collected. This study included *E. coli* isolates obtained from blood, pus, sputum, and urine specimens taken from inpatients at general hospital "X" in Bali, Indonesia.

Statistical analysis

In order to determine the cross-resistance of *E. coli* to antibiotics, an analysis of the correlation between the level of systemic antibiotic use and the percentage of *E. coli* bacteria resistance to antibiotics was carried out using the *Pearson* correlation test (p-value>0.05).

The analysis results from the Pearson test were presented as a correlation coefficient value (r) along with a significance value (p). The significance level was determined to be $p<0.05$ at a 95% CI. This shows that a p-value less than 0.05 indicates cross-resistance of *E. coli* to antibiotics. This cross-resistance was evidenced by the correlation between the level of systemic antibiotic use and the percentage of *E. coli* resistance to these antibiotics.

RESULT AND DISCUSSION

Systemic antibiotics usage

The data from Table 1 indicates that, during 2017-2020, the most common antibiotic used at general hospital "X" in Bali, Indonesia was cephalosporin (4.000 DDD/100 bed-days), and the least common was carbapenem (0.026 DDD/100 bed-days). Descriptively, it can be observed that in 2017-2020, the use of tetracycline (J01A) and quinolone (J01MA) antibiotics increased, while the use of cephalosporin (J01DB-DE), beta-lactam-penicillin (J01C), and carbapenem (J01DH) antibiotics decreased.

The most frequently used antibiotics in 2017-2020 in inpatient installation at general hospital "X" in Bali, Indonesia, was a class of cephalosporin antibiotics (4.000 DDD/100 days of treatment). This is in line with a study in China, which showed similar results, where cephalosporin antibiotics, especially the third generation, were the most widely used antibiotics during 2013-2021 (217.1 DDD/100 bed-days) (Wushouer et al., 2023). Another study in Surakarta Hospital also found the same results, which cephalosporin antibiotics (ceftriaxone) are the most widely used antibiotics in the Hospital (Farida et al., 2017). Cephalosporin antibiotics become the most widely used antibiotics because this antibiotics acts as a prophylactic antibiotic and is also the most commonly prescribed because this antibiotic has a broad spectrum, good pharmacokinetic profile, low side effects, and relatively low price (Latifah et al., 2021). Meanwhile, carbapenem antibiotics have the lowest use in this study (0.026 DDD/100 days of treatment). A study conducted in one of the Hospitals in Bali also showed similar results, where carbapenem antibiotics had the lowest use (12.59 DDD/100 days of treatment) (Meriyani et al., 2021). The carbapenem class of antibiotics is used as a last line of defense for treating severe infections caused by MDR bacteria. Because of this, the use of carbapenems is closely monitored to prevent the development of resistance to this class of antibiotics (Jorgensen & Rybak, 2018).

The use of tetracycline antibiotics in 2017-2020 showed an increase. This is similar to the study conducted in Tanzania, where this antibiotic is used to treat cholera, pelvic inflammation, and sexually transmitted diseases, which often occur in the Tanzanian (Mbwasi et al., 2020; Sangeda et al., 2021). According to the AWaRe (access, watch, reserve) classification issued by WHO, tetracycline is included in the access category, which means that this class is commonly used as the first-line agent in treating various common infectious diseases, providing good therapeutic effect and minimizing the potential of resistance, and being able to access easily and widely. This causes tetracycline to be prescribed by many doctors as the first-line therapy for patients with pneumonia, exacerbation of chronic obstructive pulmonary disease, cholera, and urinary tract infections (World Health Organization, 2022).

Descriptively, it can be observed that the use of fluoroquinolone antibiotics in this study experienced an increase. This is correlated with the high prevalence of urinary tract infections and pneumonia that attack Indonesia's population. According to the data from the Department of Health of the Republic of Indonesia in 2019, urinary tract infections in Indonesia are in the high category of 90-100 cases per 100,000 population per year or approximately 180,000 new cases per year (Prasetya et al., 2022). Data from the Ministry of Health of the Republic of Indonesia in 2017-2021 showed that pneumonia is one of the three most common diseases that attacks and causes mortality in children in Indonesia (Kementrian Kesehatan Republik Indonesia, 2022).

The results of this study also showed that, descriptively, a decrease in the use of cephalosporin, beta-lactam-penicillin, and carbapenem antibiotics has occurred. This decrease occurs because these antibiotics are included in the category of the Highest Priority Critically Important antibiotics (especially third- and fourth-generation cephalosporin) and High Priority Critically Important antibiotics (carbapenem). These antibiotics have an important role in human health, so they have the highest priority in controlling their use. The use of antibiotics in this category must be carried out carefully, and they must only be used in urgent situations or indispensable to prevent the risk of bacterial resistance to these antibiotics (World Health Organization, 2019). Moreover, a decrease in

the use of beta-lactam-penicillin antibiotics is caused by the decrease in the sensitivity of antibiotics to various bacteria (Meriyani et al., 2021).

Table 1. Data on the use of antibiotics in inpatient installation at general hospital "X" in Bali, Indonesia in 2017-2020

Code ATC/DDD	Class of Antibiotics	DDD/100 Days of Treatment				
		2017	2018	2019	2020	Total
J01DB-DE	Cephalosporin	1.180	1.041	0.920	0.859	4.000
J01MA	Fluoroquinolone	0.279	0.393	0.385	0.448	1.505
J01C	Beta Lactam- Penicillin	0.341	0.293	0.255	0.162	1.051
J01A	Tetracycline	0.029	0.034	0.052	0.034	0.149
J01DH	Carbapenem	0.009	0.006	0.004	0.008	0.026

Resistance of E. coli to antibiotics

The patterns of *E. coli* resistance to seven classes of antibiotics in 2017-2020 are presented in Table 2. The patterns of *E. coli* resistance in inpatient installation at general hospital "X" in Bali, Indonesia were resistant to ampicillin-sulbactam, aztreonam, sulfamethoxazole-trimethoprim, and ciprofloxacin. This indicates that *E. coli* have experienced MDR because they have been resistant to three or more antibiotics from different classes.

Table 2. Pattern of *E. coli* resistance to antibiotics in inpatient installation at general hospital "X" in Bali, Indonesia in 2017-2020

Class of Antibiotics	Antibiotics	Year			
		2017	2018	2019	2020
	Number of Isolate (n)	2	15	19	17
Cephalosporin	Ceftriaxone	50.00	50.00	52.60	41.20
	Ceftazidime	50.00	53.80	47.40	18.70
	Cefixime	50.00	50.00	0.00	11.80
Penicillin	Ampicillin-Sulbactam	50.00	64.30	57.90	29.40
	Piperacillin-Tazobactam	0.00	6.70	57.20	0.00
Carbapenem	Meropenem	0.00	0.00	5.30	0.00
Monobactam	Aztreonam	50.00	64.30	31.60	29.40
Sulfonamide and Trimethoprim	Sulfamethoxazole and Trimethoprim	100.00	71.40	50.00	37.50
Aminoglycoside	Gentamicin	50.00	42.90	47.40	11.80
	Amikacin	0.00	13.30	0.00	47.10
Fluoroquinolone	Ciprofloxacin	100.00	71.40	84.20	47.10

Notes: : resistance <30%: susceptible or recommended; : resistance 30-60%: intermediate or considered; : resistance >60%: resistant or not recommended

A meta-analysis stated that *E. coli* with MDR in Asian countries is high at 66.3%. The factor causing the high level of MDR in *E. coli* is the high burden of resistance to medicine, which has become the first line in treating many infectious diseases (Salleh et al., 2022).

According to the phenotypic category issued by the Centers for Disease Control and Prevention (CDC), *E. coli* in this study included in the *ESCecoli_AR* phenotypic category because these bacteria included in the intermediate resistance group to the third and fourth-generation cephalosporin antibiotics (ceftriaxone, ceftazidime, and cefepime). Moreover, these bacteria are also included in the *FQE_AR* phenotypic category because they have experienced resistance to one of the fluoroquinolone

antibiotics (ciprofloxacin) (Centers for Disease Control and Prevention, 2024). Over the last few decades, the use of quinolone and cephalosporin antibiotics to eradicate *E. coli* bacteria has continuously increased, so this incidence is often correlated with the increasing cases of *E. coli* bacteria resistance to these two classes of antibiotics (Roca et al., 2015). Based on the study conducted in Bali Hospital, the increase in the use of systemic antibiotics has a significant effect on the level or percentage of critical bacteria resistance, such as *E. coli* (Sanjaya et al., 2023).

Cross-resistance E. coli to antibiotics

The Pearson analysis can be observed in Table 3. There was a significant correlation ($p<0.05$) and a very strong correlation between the use of tetracycline and the *E. coli* resistance to meropenem ($r=0.972$) and piperacillin-tazobactam ($r=0.977$). This showed that there is a cross-resistance of *E. coli*. Cross-resistance in *E. coli* can occur due to high levels of antibiotic use. Exposure of these bacteria to antibiotics creates a selection pressure. When *E. coli* is exposed to antibiotics, there are *E. coli* that survive from this exposure, causing *E. coli* to still be able to survive, reproduce, and form defenses against this exposure, thereby producing a population of resistant *E. coli* bacteria (Bell et al., 2014; Hughes & Andersson, 2017). Antibiotic exposure significantly causes the emergence of bacterial resistance genes to antibiotics on plasmids. Besides emerging resistance genes, selection pressure is able to induce bacteria to mobilize or transfer genes between *E. coli* or other bacterial species that can cause diseases. Selection pressure becomes the main force that stimulates the production and transfer of genes in bacteria (Bengtsson-Palme et al., 2018; Larsson & Flach, 2022).

E. coli bacteria have many genes that are able to cause resistance to various classes of antibiotics. These genes can induce enzyme production, activate the efflux pump, change the target for drug action, and reduce membrane permeability so these bacteria become less sensitive to antibiotics. The main mechanism of *E. coli* to be resistant to meropenem is by producing carbapenemase or combining the extended-spectrum beta-lactamase enzyme or AmpC with structural mutations, such as outer membrane protein porin or the excessive production of efflux pump. Meanwhile, the mechanism for *E. coli* bacteria to be resistant to piperacillin-tazobactam is by producing extended-spectrum beta-lactamase enzyme or AmpC (Chang et al., 2019; Edwards et al., 2022). Several genes in *E. coli* that can produce carbapenemase enzymes are bla_{IMP}, bla_{NDM}, bla_{KPC}, bla_{VIM}, and $bla_{\text{OXA-48}}$. Besides carbapenemase, *E. coli* resistance can also be caused by producing extended-spectrum beta-lactamase enzyme as coded by $bla_{\text{CMY-2}}$ gen or AmpC and combining it with outer membrane protein porin of the bacteria as coded by OmpF and OmpC genes (Chang et al., 2019). The mechanism of *E. coli* resistant to piperacillin-tazobactam antibiotic is the same as meropenem. This similarity is because meropenem and piperacillin-tazobactam belong to the same antibiotic class, namely beta-lactam, so they both have beta-lactam ring structures. However, the difference lies in the genes encoding E. coli resistance to piperacillin-tazobactam. *E. coli* resistance to piperacilin tazobactam is coded by AmpC, bla_{TEM}, bla_{SHV}, and $bla_{\text{CTX-M-15}}$ genes (Edwards et al., 2022; Hubbard et al., 2020).

Resistance of *E. coli* bacteria to tetracycline is because these bacteria are able to activate the efflux pump. Efflux pump is induced by various genes, including *tet*(A), *tet*(B), *tet*(C), *tet*(D), *tet*(E), *tet*(J), *tet*(L), and *tet*(Y) (Poirel et al., 2018). Genes coding for extended-spectrum beta-lactamase, carbapenemase, and efflux pump activation are produced and carried by plasmids. This plasmid can be spread to another *E. coli* through gene transfer, which is the transfer of genetic information from one *E. coli* to another *E. coli*. This gene can be transferred through the mechanisms of horizontal gene transfer and vertical gene transfer between *E. coli* bacteria or different bacteria species (Bethke et al., 2022; Haaber et al., 2017).

Horizontal gene transfer includes transformation, transduction, and conjugation. In the transformation, bacteria take free DNA fragments released into the environment and then insert them into their genome, resulting in a change of characteristics or properties in the bacteria. Horizontal gene transfer by the transformation in *E. coli* has several special requirements, such as exposure to high

concentrations of Ca^{2+} or Mg^{2+} and heat shock, which is generally carried out at a temperature of 42°C for 2 minutes (Hasegawa et al., 2018; Rotinsulu et al., 2019).

Transduction is a DNA fragment transfer from one bacteria to another bacteria involving a bacteriophage mediator to change the properties of bacteria receiving DNA. The bacteriophage is able to carry DNA fragments larger than 100 kb, which is able to transfer plasmids containing the main resistance gene. Several inducing genes of extended-spectrum beta-lactamase in *E. coli*, such as $bla_{\text{CTX-M}}$, can be transferred through the transduction process. Moreover, bacteriophage is also able to transduce plasmids containing resistance genes of tetracycline, chloramphenicol, and aminoglycoside (Lerminiaux & Cameron, 2019).

Conjugation is a horizontal gene transfer through direct physical contact between donor cells and recipient cells involving the pilus. Horizontal gene transfer by conjugation is also able to cause gene recombination and form new plasmids or recombination plasmids that contain various genes that are resistant to antibiotics. This plasmid is called a multiresistance plasmid that can be spread through conjugation between bacteria populations, where plasmid recombination often occurs in pathogenic *E. coli*. Plasmid recombination has evolved in several plasmid families of IncP-1, IncW, and IncF by increasing plasmid fitness and the combination of several different genes (Rodríguez-Beltrán et al., 2021).

Several *E. coli* multi-resistance plasmids that have been found are IncHI2/IncP plasmid (225 kb) carrying resistance genes, such as *tet*(A) with bla_{CTX}, $bla_{\text{TEM-1}}$, $bla_{\text{NDM-5}}$, *sul*1, *sul*2, *dfrA*1, and *aadA*1. IncI1 plasmids (90-120 kb) carry resistance genes, such as *tet*(A) with $bla_{\text{SHV-12}}$, $bla_{\text{NDM-5}}$, $bla_{\text{KPC-2}}$, $bla_{\text{OXA-48}}$, *aadA1*, *cmlA1*, and *aadA2*. IncFIB/IncHI2 plasmids (250 kb) carry *tet*(B) gene with $bla_{\text{CTX-M-2}}$, $bla_{\text{NDM-5}}$, *sul1*, *aadA29*, *strA*, and *strB* genes. IncFIC plasmids carry *tet*(A) gene with $bla_{\text{CMY-2}}$, $bla_{\text{NDM-5}}$, $bla_{\text{KPC-2}}$, $bla_{\text{OXA-48}}$, *cmlA*, *floR*, *strA*, *strB*, *sul1*, *sul3*, and *aadA7* genes. IncFIB/IncN plasmids (40 kb) carry the *tet*(A) gene with $bla_{\text{NDM-5}}$, *sul1*, *dfrA16*, and *dfrA29*. The multiresistance plasmid can then be transferred horizontally by conjugation to fellow *E. coli* bacteria (Huang et al., 2024; Poirel et al., 2018; Zou et al., 2020).

According to a literature study, the *tet* gene, which is a gene causing resistance to tetracycline, is carried with other resistance genes on a plasmid. This indicates that using tetracycline, besides inducing the production of the *tet* gene, which is the cause of resistance to tetracycline, evidently also can induce the production of resistance genes to beta-lactam antibiotics, such as bla_{CTX}, $bla_{\text{SHV-12}}$, $bla_{\text{TEM-1}}$, $bla_{\text{CMY-2}}$, $bla_{\text{NDM-5}}$, $bla_{\text{KPC-2}}$, and $bla_{\text{OXA-48}}$, which is the gene that *E. coli* codes for resistance to extended-spectrum beta-lactam antibiotics, such as meropenem and piperacillin-tazobactam (Poirel et al., 2018). Besides horizontally, gene transfer between *E. coli* bacteria can be carried out vertically, called cell division. Vertical gene transfer refers to the process of plasmid transfer from stem cells to daughter cells during the division process. Suppose cross-resistance occurs in bacteria to antibiotics, such as tetracycline, inducing *E. coli* resistance to meropenem. In that case, it is feared that this will complicate and narrow antibiotic treatment options. Carbapenem antibiotics, such as meropenem, are the last-line treatment for multidrug-resistant gram-negative bacteria *E. coli* (Bethke et al., 2022).

This study is an ecological study that collects data at the population level, encompassing all data points that meet the inclusion criteria. Ecological study has the weakness of being unable to observe data at the individual level. If the analysis is according to population data, then the antibiotic exposure time to individuals in the population cannot be found (Aggarwal & Ranganathan, 2019). The length of antibiotic exposure can cause *E. coli* bacteria to be resistant to antibiotics (Meriyani et al., 2023; Sedláková et al., 2014).

Table 3. The correlation between antibiotics use and cross-resistance of *E. coli* to antibiotics in inpatient installation at general hospital "X" in Bali, Indonesia in 2017-2020

Code Antibiotics	The Use of Antibiotics	*E. coli* Resistance to Antibiotics	r	p
J01A	Tetracycline	Meropenem	0.972**	0.040*
		Piperacillin-Tazobactam	0.977**	0.020*
		Ceftriaxone	0.424	0.580
		Ceftazidime	0.081	0.920
		Cefixime	0.769	0.200
		Ampicillin-Sulbactam	0.728	0.270
		Aztreonam	0.525	0.480
		Sulfamethoxazole and Trimethoprim	0.371	0.630
		Gentamicin	0.184	0.820
		Amikacin	0.275	0.730
		Ciprofloxacin	0.036	0.960
J01C	Beta lactam, Penicillin	Ceftriaxone	0.765	0.240
		Ceftazidime	0.901	0.090
		Cefixime	0.718	0.280
		Ampicillin-Sulbactam	0.710	0.290
		Piperacillin-Tazobactam	0.037	0.960
		Meropenem	0.067	0.930
		Aztreonam	0.707	0.290
		Sulfamethoxazole and Trimethoprim	0.208	0.790
		Gentamicin	0.907	0.090
		Amikacin	0.859	0.140
		Ciprofloxacin	0.902	0.090
J01DB-DE	Cephalosporin	Ceftriaxone	0.486	0.290
		Ceftazidime	0.698	0.300
		Cefixime	0.851	0.150
		Ampicillin-Sulbactam	0.442	0.560
		Piperacillin-Tazobactam	0.365	0.640
		Meropenem	0.376	0.620
		Aztreonam	0.706	0.290
		Sulfamethoxazole and Trimethoprim	0.420	0.580
		Gentamicin	0.703	0.290
		Amikacin	0.644	0.360
		Ciprofloxacin	0.794	0.210
J01DH	Carbapenem	Ceftriaxone	0.620	0.380
		Ceftazidime	0.369	0.600
		Cefixime	0.487	0.510
		Ampicillin-Sulbactam	0.625	0.380
		Piperacillin-Tazobactam	0.903	0.090
		Meropenem	0.849	0.150
		Aztreonam	0.102	0.910
		Sulfamethoxazole and Trimethoprim	0.668	0.330
		Gentamicin	0.383	0.620
		Amikacin	0.416	0.580
		Ciprofloxacin	0.102	0.890

Table 3. The correlation between antibiotics use and cross-resistance of *E. coli* to antibiotics in inpatient installation at general hospital "X" in Bali, Indonesia in 2017-2020 (continue)

Code Antibiotics	The Use of Antibiotics	*E. coli* Resistance to Antibiotics	r	p
J01MA	Quinolone	Ceftriaxone	0.577	0.420
		Ceftazidime	0.647	0.350
		Cefixime	0.575	0.430
		Ampicillin-Sulbactam	0.364	0.640
		Piperacillin-Tazobactam	0.101	0.890
		Meropenem	0.079	0.920
		Aztreonam	0.398	0.600
		Sulfamethoxazole and Trimethoprim	0.618	0.380
		Gentamicin	0.768	0.230
		Amikacin	0.766	0.230
		Ciprofloxacin	0.933	0.070

Notes: * = significant correlation; ** = very strong correlation

CONCLUSION

Cephalosporin antibiotics were the most frequently used during 2017-2020, while carbapenem was the least commonly used. The category of *E. coli* resistance in this study was MDR, *ESCecoli_AR*, and *FQE_AR*. The use of tetracycline is significantly correlated with the increased of *E. coli* resistance to meropenem and piperacillin-tazobactam, indicating that the level of use of one antibiotic can influence *E. coli*'s resistance to others.

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