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Antibiotic consumption and resistance: a 3-years ecological study for four critical groups of bacteria in a general regional hospital

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ABSTRACT

Pseudomonas aeruginosa, *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae* are the most critical groups of multi-drug resistant (MDR) bacteria that cause a threat in hospitals. This study identified the trend of antibiotic consumption, antibiotic resistance pattern, and the relationship between antibiotic consumption and antibiotic resistance in a critical group of bacteria in a general regional hospital. This ecological study was based on retrospective data from inpatient databases in a general regional hospital over three years (2017-2019). The trend for annual antibiotic consumption over 2017-2019 was defined as defined daily doses/100 bed-days. The relationship between total antibiotic consumption and the percentage of antibiotic resistance among four isolated critical bacteria was explored in time series analysis and linear regression. The most frequently used antibiotic was ampicillin (220.33 DDD/100 bed-days), ciprofloxacin (126.86 DDD/100 bed-days), and ampicillin-sulbactam (126.34 DDD/100 bed-days). There was a significant relationship between antibiotic consumption (ampicillin, ampicillin-sulbactam, ceftazidime, gentamicin, amikacin, and ciprofloxacin) in DDD/100 bed-days and antibiotic resistance in *E. coli*, *K. pneumoniae*, and *P. aeruginosa* ($p<0.05$) but not statically significant in *A. baumannii* ($p=0.062$). The annual usage fluctuated or remained stable, with no statistically significant trends change. The relationship between antibiotic consumption and antibiotic resistance was significant in three out of four critical groups of bacteria.

Keywords: *Acinetobacter baumannii*, *antibiotic consumption*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*

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INTRODUCTION

The increasing level of antibiotic resistance threatens the Sustainable Development Goals (SDGs). This phenomenon significantly influences economic, social, and healthcare changes (Gajdács et al., 2021; Laxminarayan et al., 2013). Antibiotic resistance is one of the main global health concerns that can lead to increased financial burden, length of stay, morbidity, and mortality. Misuse, overuse of antibiotics, and high levels of antibiotic consumption are considered to exert selective pressure, thereby accelerating antibiotic resistance and leading to the emergence of multi-drug resistant (MDR) bacteria (Amaha et al., 2020; Mascarello et al., 2017; Shafiq et al., 2016).

Pseudomonas aeruginosa, *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae* can cause healthcare-associated infections and fatal nosocomial infections such as bloodstream infections, surgical site infections, and pneumonia (Kousovista et al., 2021; Veličković–Radovanović et al., 2015). They are the most critical groups of MDR bacteria that cause a threat in hospitals. Several studies showed that *A. baumannii* is significantly resistant to meropenem, cefepime, and ciprofloxacin correlated with meropenem, cefepime, and ciprofloxacin use (Kousovista et al., 2021). *P. aeruginosa* was resistance to ciprofloxacin, meropenem, and cefepime. Gentamycin, ciprofloxacin, and ceftriaxone resistance were found in *E. coli* isolates. *K. pneumoniae* isolates showed resistance to ceftazidime, amikacin, ceftriaxone, and ciprofloxacin. The increasing antibiotic resistance was correlated to antibiotic consumption (JoSeph et al., 2015; Veličković–Radovanović et al., 2015).

A previous study in Indonesia's general regional hospital analyzed the relationships between antibiotic consumption and antibiotic resistance to coagulase-negative staphylococci (Meriyani et al., 2021). In Indonesia, there are no studies on the relationship between antibiotic consumption and antibiotic resistance in a critical group of MDR bacteria. The sensitivity of antibiotics to bacteria differs by region, and the regional reported antibiotic resistance varies widely due to differences in environment and antibiotic consumption (Tao et al., 2017). The local antibiotic resistance pattern is essential to confirm the choice of antibiotics against critical groups of MDR bacteria (Luyt et al., 2014; Rezaie et al., 2016). Therefore, this study identified the relationship between antibiotic consumption and antibiotic resistance in a critical group of bacteria (*Pseudomonas aeruginosa*, *Acinetobacter baumannii, Escherichia coli,* and *Klebsiella pneumoniae*) in a general regional hospital. They are the most bacteria that cause infection in general hospital. Information about the trend of antibiotic consumption, antibiotic resistance pattern, and the relationship between antibiotic consumption and antibiotic resistance in a critical group of bacteria can be used to control antibiotic usage and antibiotic resistance. Knowledge of this relationship is needed to decrease the irrationality of antibiotic consumption.

METHOD

Methods

This was an ecological study based on retrospective data from inpatient databases in Indonesia's general regional hospital, over three years, from January 1st, 2017, until December 31st, 2019. This is a 588-beds tertiary care hospital as a regional referral medical centre. The bed occupancy rate (BOR) was 0.88 in 2017, 0.84 in 2018, and 0.85 in 2019. This study was approved by the general regional hospital's institutional review board (IRB) and the hospital research committee on June 2020 (070/5035/RSD/2020). The committee waived the informed consent requirement because this was a retrospective study without human subjects, and all the secondary data would be used.

Data Analysis

Antibiotic consumption

Antibiotic consumption was collected from electronic pharmacy records in a general regional hospital, from 2017 to 2019. The annual antibiotic consumption was defined as the number of defined daily doses/100 bed-days (DDD/100 bed-days) based on the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification. DDD/100 bed-days is calculated by

dividing the numbers of DDDs by patients-days and multiplying by 100 Only antibiotics for systemic treatment (oral and injectable) in ATC class J01 were used, and the other antibiotic agents as a topical were excluded in this study.

Microbial resistance data

Data on the susceptibility of four critical bacteria (*P. aeruginosa*, *A. baumannii*, *E. coli*, and *K. pneumoniae*) to antibiotics were collected from the antibiogram. The antibiogram susceptibility results were based on the Clinical and Laboratory Standards Institute (CLSI) with the disk diffusion method. The database included all positive clinical specimens from sputum, blood, and urine. The percentage of antibiotic resistance was defined as the percentage of resistant bacterial isolates compared to the total number of isolates, including isolates from urine, blood, pus, and sputum culture. Results for susceptibility were susceptible to antibiotics (S), intermediately resistant (I), and resistant (R). In this study, intermediately resistant and resistant strains were considered resistant (Center for Disease Control and Management, 2019).

Statistical analysis

The trend for annual antibiotic consumption over 2017-2019 was explored by time series analysis using linear regression, which assesses the changes in trends (i.e., slopes) of the response (i.e., antibiotic consumption) during the study period. Correlation and linear regression analyses were used to analyze the relationship between total antibiotic consumption (ampicillin, ampicillin-sulbactam, ceftazidime, gentamicin, amikacin, and ciprofloxacin), described as DDD/100 bed-days as the independent variable, and the percentage of antibiotic resistance among four isolated critical bacteria as the dependent variable. All statistical tests were considered statistically significant at a p-value < 0.05. The Statistical Program for Social Science (SPSS) 26.0 (IBM Corporation, USA) was used for all statistical analyses (Barton & Peat, 2014; George & Mallery, 2019).

RESULT AND DISCUSSION

Trends in antibiotic consumption

The overall trend of annual antibiotic consumption over 2017-2019 is presented in Table 1. The most frequently used antibiotic in this study was ampicillin (220.33 DDD/100 bed-days) from total antibiotic consumption during 2017-2019, followed by ciprofloxacin (126.86 DDD/100 bed-days) and ampicillin-sulbactam (126.34 DDD/100 bed-days). However, ampicillin, ampicillin-sulbactam, and ceftazidime consumption decreased from 2017 to 2019. Time series analysis demonstrated that the annual usage fluctuated or remained stable, with no statistically significant changes in trends (p>0.05). During the study period, the trend of gentamicin indicated an increasing trend in DDD/100-bed days, although this was not statistically significant. Amikacin and ciprofloxacin are given a stable trend, although slopes showed an increasing trend.

Data on the consumption of antibiotics in this study show that the most frequently used antibiotic with an increasing trend was ciprofloxacin (126.86 DDD/100 bed-days and *slope* (b) = 0.220). Based on data from India, Bangladesh, Sri Lanka, Thailand, and Indonesia, the World Health Organization (WHO) Report on Surveillance of Antibiotic Consumption 2016 - 2018 indicated that South-East Asia had a high consumption of cephalosporins and quinolones (World Health Organization, 2018). A cross-sectional audit of antibiotic prescribing practices at hospitals in 53 countries, including Asia, found that penicillin with a β-lactamase inhibitor and fluoroquinolone (levofloxacin and ciprofloxacin) was the most commonly prescribed in the east and south Asia in 2015. A high level of fluoroquinolone consumption in hospitals is associated with the prevalence of pneumonia (Versporten et al., 2018). Based on surveillance data from the Ministry of Health, Republic of Indonesia, from 2017 until 2019, pneumonia was one of Indonesia's three most common diseases (Kementerian Kesehatan Republik Indonesia, 2020; Ministry of Health, 2018).

In addition, the high prevalence of antibiotic-resistant bacteria in Southeast Asia is associated with increased consumption of broad-spectrum antibiotics, such as ceftriaxone, ceftazidime, cefotaxime,

levofloxacin, ampicillin, gentamicin, and meropenem (Honda et al., 2017; Lee et al., 2013; Versporten et al., 2018). The potential nephrotoxicity caused by aminoglycosides is related to the trend of annual usage of gentamicin and amikacin (Lee et al., 2013). However, in this study, ampicillin, and ceftazidime consumption trend decreased from 2017 to 2019 (Table 1). Moreover, some studies suggest that trend of annual antibiotic consumption fluctuating is most likely related to multifactorial, such as physician's attitudes and knowledge about bacterial infection and antibiotic prescription, lack of well-established infectious disease and treatment, and the lack of infectious diseases experts to manage the program for antimicrobial stewardship (Honda et al., 2017; Kim et al., 2018).

Antibiotic resistance

During the study period, 266 isolates from the four critical bacteria were separated from the clinical sample. The pattern of antibiotic resistance in four critical bacteria is described in Table 2. The percentage of antibiotic resistance was highly resistant (more than 60%) are not recommended for therapy. *K. pneumonia is* only resistant to ampicillin and a combination of sulfamethoxazole and trimethoprim. *E. coli* showed resistance to ampicillin, ampicillin-sulbactam, cefotaxime, ceftriaxone, and ciprofloxacin. *P. aeruginosa* was resistant to ampicillin, ampicillin-sulbactam, piperacillin-tazobactam, aztreonam, and nitrofurantoin. The antibiotic resistance pattern in *A. baumannii* is similar to *P. aeruginosa*, except for piperacillin-tazobactam and nitrofurantoin. In addition, *A. baumannii* was resistant to ceftriaxone.

The relationship between antibiotic consumption (ampicillin, ampicillin-sulbactam, ceftazidime, gentamicin, amikacin, and ciprofloxacin) in DDD/100 bed-days and antibiotic resistance percentages from the four critical bacteria is summarized in Figure 1. There was a significant relationship between DDD and antibiotic resistance in *E. coli* (p-*value*=0.038; r= 0.837) (Figure 1A), *K. pneumoniae* (p-*value*=0.031; r= 0.851) (Figure 1C), and *P. aeruginosa* (p-*value*=0.039; r= 0.833) (Figure 1D). The coefficient correlation (r) between antibiotic consumption (DDD/100 bed-days) and antibiotic resistance percentages in *A. baumannii* has a high correlation (r=0.790) (Figure 1B) but is not statically significant.

Antibiotic consumption may increase selective pressure on certain classes of antibiotics. Although antibiotic consumption in hospitals is much lower than in the community, the intensity of use ensures a high rate of antibiotic resistance in the hospitals (Cižman & Srovin, 2018). Previous studies used aggregated population-level data to investigate the correlation between antibiotic consumption and antibiotic resistance in *P. aeruginosa*, *A. baumannii*, *E. coli*, and *K. pneumoniae* (JoSeph et al., 2015; Kousovista et al., 2021; Mladenovic-Antic et al., 2016; Sedláková et al., 2014). Several studies suggested that increased consumption of antibiotics has a negative correlation and is not statically significant with resistance rate (Kim et al., 2018; Mascarello et al., 2017). In our research, the relationship between antibiotic consumption (DDD/100 bed-days) and antibiotic resistance in *P. aeruginosa*, *E. coli*, and *K. pneumoniae* was statically significant but not in *A. baumannii* (Figure 1). This indicates that antibiotic resistance in hospitals varies commonly due to differences in environment and antibiotic consumption and is influenced by multi-factors, such as misuse and overuse of antibiotics, inappropriate prescribing, horizontal gene transfer, and resistance mechanisms that might differ between species (Tao et al., 2017; Ventola, 2015).

Interestingly, in this study, *P. aeruginosa*, *A. baumannii*, and *E. coli* were MDR species, except for *K. pneumoniae* (Table 2). MDR is defined as resistance to at least one antibiotic in three or more antibiotic classes (Center for Disease Control and Management, 2019). WHO reported *Acinetobacter*, *Pseudomonas*, and some Enterobacteriaceae (including *Klebsiella* and *E. coli*) as critical MDR bacteria resistant to various antibiotics, posing a threat in hospitals (World Health Organization, 2017). *P.* aeruginosa, *A. baumannii*, *E. coli*, and *K. pneumoniae* produce antibiotic-inactivating enzymes, such as β-lactamases. This enzyme can break the amide bond of the β-lactam ring, which results in the inactivation of β-lactam antibiotics. This is closely related to the contribution of the *amp*C gene encoding the β-lactamases enzyme (Pang et al., 2019; Sedláková et al., 2014). Through limited outer

membrane permeability and efflux systems that push antibiotics out of the cell, *P.* aeruginosa and *A. baumannii* have a high level of resistance to most antibiotics. In addition, the ability of *P.* aeruginosa and *A. baumannii* to produce biofilm contributes to antibiotic resistance (Gedefie et al., 2021; Pang et al., 2019). Moreover, *E. coli* and *K. pneumoniae* are the main bacteria that produce extended-spectrum β-lactamases (ESBLs). Like β-lactamases, the ESBLs can break down penicillin, cephalosporins, and fluoroquinolones. Through the production of ESBLs, *E. coli* and *Klebsiella pneumoniae* become highly resistant to antibiotics (Brolund, 2014; Dupouy et al., 2019; Mansouri et al., 2019; McDanel et al., 2017).

This study has an ecological design with some potential limitations, such as being based on aggregated data. Although DDD measurements are international tools for quantifying antibiotic use, calculating antibiotic consumption using DDD measurements only measures aggregated-population levels. The analysis of the correlation between antibiotic consumption and antibiotic resistance using an aggregated-population level has the potential for ecological bias because resistance selection pressure arises at the individual level (Guo et al., 2015; Plüss-Suard et al., 2013; Zou et al., 2015). Moreover, this study was based on a single hospital setting in Indonesia. Thus, studies with multicenter designs and longer surveillance periods are needed to explain the correlation between antibiotic consumption and antibiotic resistance.

Table 1. Annual usage trends of inpatient antibiotic consumption at a general regional hospital, 2017-2019

ATC Code	Antibiotics	Antibiotic consumption (DDDs/100 bed-days) per year				Time series analysis		
		2017	2018	2019	Total 2017-2019	Slope (b)	*p-value*	Trend
J01CA01	Ampicillin	80.04	78.05	62.24	220.33	-8.900	0.268	Decreasing
J01CR01	Ampicillin-sulbactam	45.07	40.82	40.45	126.34	-2.310	0.287	Decreasing
J01DD02	Ceftazidime	15.77	14.87	11.67	42.31	-2.050	0.199	Decreasing
J01GB03	Gentamicin	22.45	20.82	27.03	70.30	2.290	0.496	Increasing
J01GB06	Amikacin	15.45	20.53	17.37	53.35	0.960	0.756	Stable
J01MA02	Ciprofloxacin	40.43	45.56	40.87	126.86	0.220	0.951	Stable

Table 2. The pattern of antibiotic resistance in four critical bacteria at a general regional hospital, 2017-2019

ANTIBIOTIC	ANTIBIOTIC RESISTANCE PERCENTAGES (%)			
	E. coli	***A. baumanii***	***K. pneumoniae***	***P.aeruginosa***
	(N=83)	**(N=70)**	**(N=64)**	**(N=49)**
J01A-TETRACYCLINES				
J01AA-Tetracyclines				
J01AA12-Tigecycline	0.00	5.71	0.00	50.00
J01C-BETA-LACTAM, PENICILLIN				
J01CA-Penicillins with extended-spectrum				
J01CA01-Ampicillin	96.39*	100.00*	100.00*	100.00*
J01CR-Combinations of penicillins				
J01CR01-Ampicillin-Sulbactam	81.82*	100.00*	36.40	100.00*
J 01CR05-Piperacillin-Tazobactam	24.00	5.71	-	100.00*
J01D- OTHER BETA-LACTAM				
J01DB-First-generation cephalosporins				
J01DB04-Cefazolin	100.00*	-	-	-
J01DD-Third-generation cephalosporins				
J01DD01-Cefotaxime	63.64*	-	14.00	-
J01DD02-Ceftazidime	45.45	41.43	37.50	32.70
J01DD04-Ceftriaxone	63.63*	89.39*	25.50	-
J01DE-Fourth-generation cephalosporins				
J01DE01-Cefepime	40.91	54.55	25.00	18.40
J01DF-Monobactams				
J01DF01-Aztreonam	59.09	100.00*	27.30	69.40*
J01DH-Carbapenems				
J01DH02-Meropenem	13.64	0.00	-	50.00
J01DH03-Ertapenem	4.55	-	0.00	-
J01E-SULFONAMIDES AND TRIMETHOPRIM				
J01EE-Combinations of sulfonamides and trimethoprim				
J01EE01-Sulfamethoxazole and trimethoprim	43.18	5.71	100.00*	50.00
J01G-Aminoglycoside				
J01GB03-Gentamicin	40.91	21.43	35.94	50.00
J01GB06-Amikacin	2.41	11.43	0.00	6.10
J01M-Quinolone				
J01MA02-Ciprofloxacin	79.55*	40.00	37.50	57.10
J01X-OTHER ANTIBACTERIALS				
J01XE-Nitrofuran derivatives				
J01XE01-Nitrofurantoin	43.18	0.00	-	100.00*

* The percentage of antibiotic resistance was highly resistant (more than 60%)

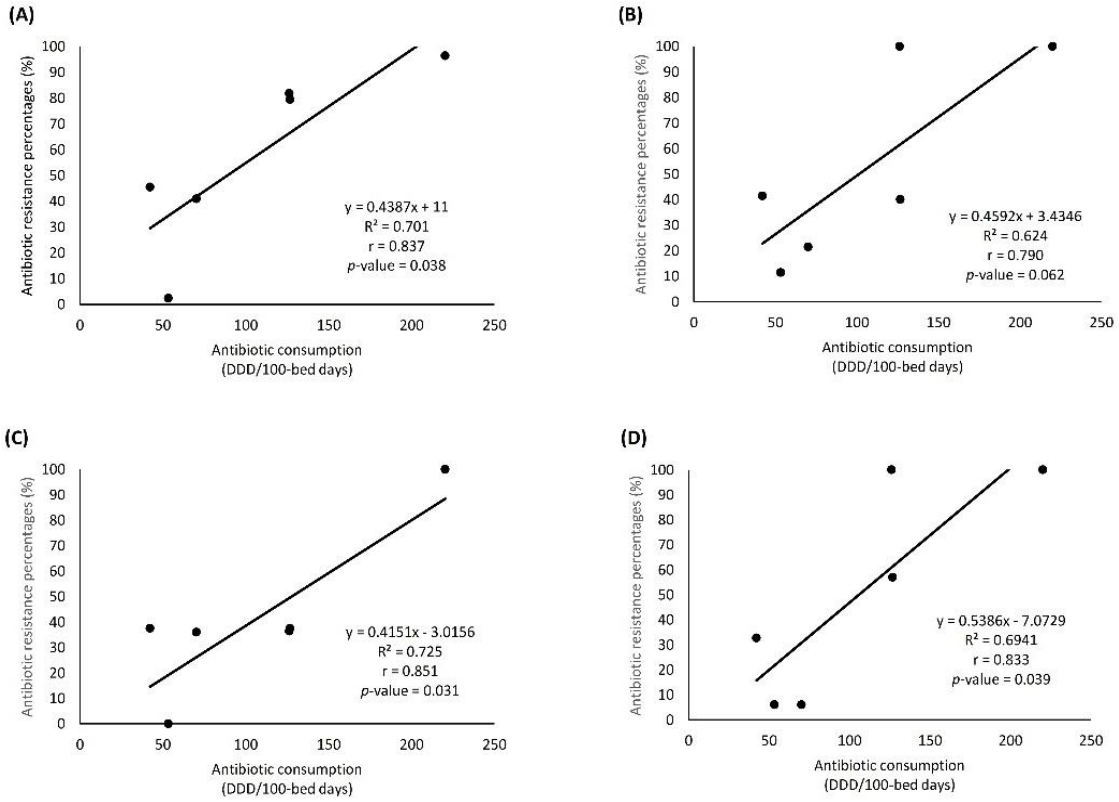

Figure 1. Linear regression analysis of antibiotic consumption and antibiotic resistance percentage in critical group bacteria. (A) *E. coli*; (B) *A. baumanii*; (C) *K. pneumoniae*; (D) *P. aeruginosa*

CONCLUSION

The overall trend of annual antibiotic consumption during the three years fluctuated; the most frequently used antibiotic with an increasing trend was ciprofloxacin. *P. aeruginosa*, *A. baumannii*, and *E. coli* as critical MDR bacteria resistant to various antibiotics. There was a significant relationship between antibiotic consumption (DDD/100 bed-days) and antibiotic resistance in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, but not statically significant in *A. baumannii*. Antibiotic resistance in hospitals varies commonly due to differences in environment and antibiotic consumption. It is influenced by multi-factors, such as misuse and overuse of antibiotics, inappropriate prescribing, horizontal gene transfer, and resistance mechanisms that might differ between species. This study has an ecological design with some potential limitations, such as being based on aggregated data, although DDD measurements are international tools for quantifying antibiotic use. However, information about the trend of antibiotic consumption, antibiotic resistance pattern, and the relationship between antibiotic consumption and antibiotic resistance in a critical group of bacteria can be used to control antibiotic usage, antibiotic resistance, and decrease the irrationality of antibiotic consumption.

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