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Antibiotic Consumption and Resistance Pattern of 3 Coagulase-Negative Staphylococci Species: An Ecological Study

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ABSTRACT

A group of coagulase-negative staphylococci (CoNS) was historically classified as a nonpathogenic bacteria. Over the last few decades, nosocomial infections caused by CoNS as opportunistic pathogens have increased and become one of the major nosocomial infections. The aim of this study was to identify the relationship between the use of an antibiotic agent for CoNS in Bali's regional public hospital and the development of antibiotic resistance during 3 years period. This study was a retrospective ecological study of antibiotic resistance and antibiotic consumption secondary data collected prospectively. The study was conducted using three years of inpatient data. Susceptibility of CoNS to antibiotics was obtained from the hospital antibiogram of all isolates from 2017 to 2019. Sensitivity results in the antibiogram were based on the standards provided by the Clinical and Laboratory Standards Institute (CLSI) with the disk diffusion method. Antibiotic consumption in DDDs/100 bed-days was calculated. The relationships between DDDs/100 bed-days of each antibiotic and rates of antibiotic resistance of each resistant strain of CoNS were tested using Spearman correlation and logistic regression. There was no significant correlation between antibiotic consumption (DDD) and the percentage of antibiotic resistance among the three CoNS species (p>0.05). However, this study found there was an inverse relationship between DDD and antibiotic resistance in *Staphylococcus hominis* species (OR = 0.063; CI [0.004-0.915]; p=0.043). We conclude that no significant correlation between antibiotic consumption and resistance to the 3 CoNS species. There needs to be further research to identify antibiotic consumption, antibiotic resistance, and other factors affecting antibiotic resistance.

Keywords: antibiotic consumption, antibiotic resistance, ecological study, coagulase-negative staphylococci

INTRODUCTION

A group of coagulase-negative staphylococci (CoNS) was historically classified as nonpathogenic bacteria. Over the last few decades, the widespread use of implants and increasing number of severely debilitated patients in hospitals have given a burst to the spread of nosocomial infections caused by CoNS as opportunistic pathogens. Moreover, due to the patient and procedure-related changes, CoNS become one of the major nosocomial pathogens. Furthermore, as nosocomial pathogens, increasing rates of antibiotic resistance are an even greater problem for CoNS than for coagulase-positive staphylococci, for instance, *S. aureus*, leading to limited therapeutic options (Becker, 2014). *Staphylococcus epidermidis, Staphylococcus hominis, and Staphylococcus haemolyticus* are the most common CoNS species (Heilmann, *et al., 2019)*. In this context, CoNS plays a primary role as an important group of gram-positive coccoid bacteria that can lead to increased mortality. In recent years, reports of CoNS infection-induced bacteremia, septicemia, endophthalmitis, and endocarditis have increased rapidly (Bhatt *et al.*, 2016; Von Eiff, *et al.*, 2006). The prevalence of septicaemia in Indonesia does not have accurate data. The prevalence ranged from 15 to 37,2%, with a mortality rate of 37-80% caused by septic shock. In Indonesia, especially in regional public hospitals in Bali, the most common bacteria causing septicemia are CoNS such as *S. haemolyticus, S. hominis, and S. epidermidis* (Mahendra *et al*., 2016;

Wahyuni and Nurahmi, 2016). Because of the high prevalence and mortality rate of CoNS, accurate species identification and determination of antibiotic resistance profiles are important for treating these infections (Bhatt *et al*., 2016).

Several CoNS species were found to be resistant to penicillin, but were susceptible to glycopeptides and linezolid and showed resistance to fluoroquinolones, aminoglycosides, and macrolides (Bhatt *et al*., 2016). Some CoNS species are more resistant to commonly used antimicrobial agents than others. In this study, we identified the relationship between the use of an antibiotic agent for CoNS in Bali's regional public hospital and the development of antibiotic resistance during 3 years period. To date, there have been limited studies on the relationship between antibiotic use and antibiotic resistance in CoNS, especially in Bali. Information about antibiotic resistance patterns for CoNS can be used as an early detection tool for irrational antibiotic administration and as a source of information in controlling antibiotic resistance. A study on antibiotic use is needed to improve the rationality of antibiotic use. In addition, this study also provides benefits in determining the right antibiotic in infectious diseases caused by CoNS.

MATERIAL AND METHODS

This study was conducted at a regional public hospital in Bali, Indonesia, with 588 beds of tertiary care that serves as a regional referral medical center. This study was a retrospective analysis of antibiotic resistance and antibiotic consumption secondary data collected prospectively. The study was conducted over three years (January 1st, 2017 to December 31th 2019) of inpatient data. An institutional review board (IRB) exemption application was submitted for this study in May 2020 since the study involved no human subjects and only de-identified secondary data would be utilized. The regional public hospital IRB and the hospital research committee approved this study in June 2020.

Antimicrobial resistance data

Data on the susceptibility of CoNS to antibiotics were obtained from the hospital antibiogram of all isolates from 2017 to 2019. Sensitivity results in the antibiogram were based on the standards provided by the Clinical and Laboratory Standards Institute (CLSI) with the disk diffusion method. Susceptibility results consisted of susceptibility to antibiotics (S), intermediate resistance (I), and resistance (R). In our study, intermediately resistant and resistant strains were considered resistant. Resistance was expressed as a percentage of the strains among all isolated strains. In addition, multi-drug resistance was defined as being non-susceptible to at least one antibiotic in three or more drug classes (Center for Disease Control and Management, 2019).

Antibiotic prescription.

Antibiotic prescription inpatient data were extracted from electronic pharmacy records at a regional public hospital. The use of antibiotics in DDDs/100 bed-days was calculated for each year using the ATC/DDD index. Consumption data were shown as drug utilization 90% (DU90%) profiles for three years period. DU90% can be used to analyze the quality of drug prescription and analyze the number of drugs accounting for 90% of drug use (Pradipta *et al*., 2015). In this study, antibiotics were ranked in order of utilization volume in DDDs. Antibiotics were analyzed that accounted for 90% of the volume in DDDs. Within this DU90% segment, data were also included into bacterial resistance to the drugs.

Statistical analysis.

DDDs/100 bed-days of antibiotics from 2017 to 2019 are presented as the number of doses. For each antibiotic, the association between DDDs/100 bed-days and the three consecutive study years, 2017 to 2019, were analyzed using descriptive statistics, and the most antibacterial use segment was identified by the DU90% method.

The association between the percentage of resistance and the three consecutive study years, 2017 to 2019, was analyzed using descriptive statistics. Finally, the relationships between DDDs/100 bed-days of each antibiotic and rates of antibiotic resistance of each resistant strain of CoNS were tested using Spearman rank correlation and logistic regression. All correlation tests were conducted using a significance level set at $P < 0.05$ and odds ratio (OR) with 95% CI. All analyses were performed using SPSS software (Version 22.0 SPSS IBM, USA).

RESULT AND DISCUSSION

Antibiotic consumption data for the J01 class in the inpatient regional public hospital was 488.35 DDD/100 bed-days in 2017, 512.84 DDD/100 bed-days in 2018, and 511.76 DDD/100 bed-days in 2019. There were seven antibiotics that included DU90% (Table I).

Table I. Antibiotic consumption in the inpatient regional public hospital during 2017-2019

Antibiotics	DDDs/100 bed-days 2017	DDDs/100 bed-days 2018	DDDs/100 bed-days 2019	DDDs/100 bed-days total	% DDD	Segmen DU
Levofloxacin	103.55	112.23	121.01	336.79	22.26	90%
ceftriaxone	100.45	107.97	122.42	330.84	21.87	
Ampicilin	80.04	78.05	62.24	220.33	14.56	
Cefotaxime	55.76	58.45	62.15	176.36	11.66	
Ciprofloxacin	40.43	45.56	40.87	126.86	8.38	
Ampicillin-sulbactam	45.07	40.82	40.45	126.34	8.35	
Gentamicin	22.45	20.82	27.03	70.30	4.65	
Amikacin	15.45	20.53	17.37	53.35	3.53	10%
Ceftazidime	15.77	14.87	11.67	42.31	2.80	
Azithromycin	5.93	4.86	6.09	16.88	1.12	
Meropenem	3.45	8.68	0.46	12.59	0.83	
Total	488.35	512.84	511.76			

Table II. Correlation between antibiotic use and antibiotic resistance

	The use of antibiotic (DDD/100 days)		
		r	p
Percentage of antibiotic resistance	*Staphylococcus epidermidis*	-0.128	0.650
	Staphylococcus haemolyticus	-0.143	0.610
	Staphylococcus hominis	-0.478	0.071

These antibiotics belong to the beta-lactam group, quinolone, and aminoglycoside groups. The most used antibiotic in the hospital based on DDD parameters during 3 years period was levofloxacin. DDD levofloxacin and cefotaxime rose over 3 years. On the other hand, ampicillin-sulbactam use dropped slightly during this period.

Data from the World Health Organization (WHO) Report on Surveillance of Antibiotic Consumption 2016 – 2018 found a high level of consumption of cephalosporins and quinolones in South-East Asia based on data from five countries (Bangladesh, India, Indonesia, Sri Lanka, and Thailand) and a very high level of consumption of third-generation cephalosporins in all states in India. This is similar to the results of our study in which cephalosporins and quinolones were the most frequently used antibiotics during 2017-2018. Until now, there is no available report about antibiotic consumption during 2019 by the WHO in South-East Asia (World Health Organization, 2018). A study at GSL General Hospital, India in November 2019 found that the most frequently used antibiotic classes were penicillin, third-generation cephalosporins, and quinolones. In this study, the rate of utilization of antibiotics was found to be 78% (Kumar *et al.*, 2020). The study about "Evaluation Of Antibiotic Use In 2018 At The Kebayoran Baru Primary Health Care, Indonesia, Using The Anatomical Therapeutic Chemical/ Defined Daily Dose Method", reported that 4 out of 10 antibiotics (40%) (i.e., amoxicillin, ciprofloxacin, cefadroxil, and thiamphenicol) were included in the DU90% segment list for the patients at Kebayoran Baru Primary Health Care in 2018. This is slightly different from the distribution data of DU90% of antibiotics in our study in which levofloxacin, ceftriaxone, ampicillin, cefotaxime, ciprofloxacin, ampicillin-sulbactam, and gentamicin were included in the DU90% segment list.

The high use of antibiotics consumption has the potential to increase antibiotic resistance. Antibiotics that are included in the DU90% segment must be evaluated for rational use to minimize the risk of resistance. The identification of antibiotics in the DU 90% segment can also be used as planning data for providing drugs for the next period (Kumar *et al.*, 2020).

The correlation between antibiotic consumption (DDD/100 patients days) and antibiotic resistance (Table II). Antibiotic consumption were negatively correlated with antibiotic resistance of *S. Epidermidis* (r=-0.128), *S. Haemolyticus* (r=-0.143), and *S. Hominis* (r=-0.478).

However, based on Spearman correlation analysis (Table II), in general, there was no significant correlation between antibiotic consumption (DDD/100 patients days) and the percentage of antibiotic resistance among the three CoNS species ($p>0.05$). The results from several studies indicate a complex relationship between antibiotic use and antibiotic resistance, for example, antibiotic consumption negatively correlated with antibiotic resistance. It suggested that antibiotic resistance is not only related to antibiotic consumption (DDD/100 patient's days). It is difficult to explain with the available data, so further research is needed to explain this association (Hu *et al*., 2020; Popović *et al*., 2020).

Three CoNS species that were observed consisted of *S. epidermidis, S. haemolyticus,* and *S. hominis*, with 50 isolates. Based on the results (Figures 1, 2, and 3), three types of CoNS have different resistance patterns during the 3 years. Different species of CoNS showed different susceptibility to antibiotics and resistance patterns (Azimi *et al*., 2019). Figure 1 shows the pattern of resistance percentage of *S. epidermidis* to ampicillin-sulbactam, cefotaxime, ciprofloxacin, gentamicin, and levofloxacin at a regional public hospital in Bali during 2017-2019. In general, the percentage of resistance decreased from 2017 to 2019. *S. epidermidis* was the most prevalent species among other CoNS species, with the highest percentage of slime positivity. Slime is a mucopolysaccaride that plays a big role in bacterial colonization and spread within hospital environment (Koagulaz and Karşılaştırılması, 2014; Koksal *et al*., 2009).

The pattern of resistance percentage of *S. haemolyticus* to ampicillin-sulbactam, cefotaxime, ciprofloxacin, gentamicin, and levofloxacin at a regional public hospital in Bali during 2017-2019 (Figure 2). In general, the percentage of resistance decreased from 2017 to 2019. *S. haemolyticus* had a percentage of slime positivity less than *S. epidermidis* (Koagulaz and Karşılaştırılması, 2014; Koksal *et al*., 2009). The pattern of resistance percentage of *S. hominis* to ampicillin-sulbactam, cefotaxime, ciprofloxacin, gentamicin, and levofloxacin at a regional public hospital in Bali during 2017-2019 (Figure 3). In general, the percentage of resistance decreased from 2017 to 2019. Furthermore, *S. hominis* has the lowest percentage of resistance compared to the other two CoNS species. Moreover, *S. hominis* has the lowest percentage of slime positivity compared with two other CoNS species (Koagulaz and Karşılaştırılması, 2014; Koksal *et al*., 2009). The decrease in the percentage of resistance of yje three species CoNS during 3 years was caused by multi-factors, for instance: lack of infection control, common use of antibiotics, irrational use of antibiotics, common use of antibiotics obtained as over the counter medicine in developing countries, etc (Deyno, *et al*., 2018).

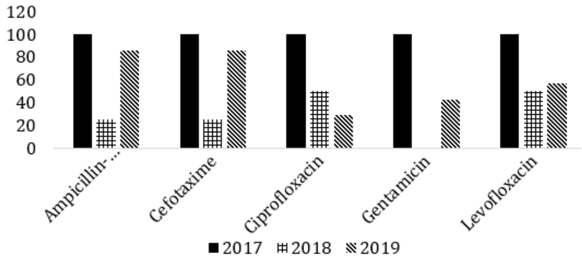

Figure 1. The pattern of antibiotic resistance in *Staphylococcus epidermidis*

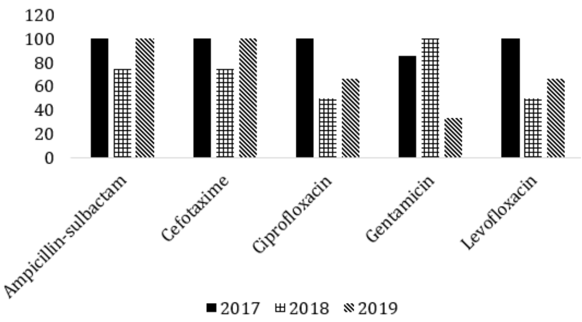

Figure 2. The pattern of antibiotic resistance in *Staphylococcus haemolyticus*

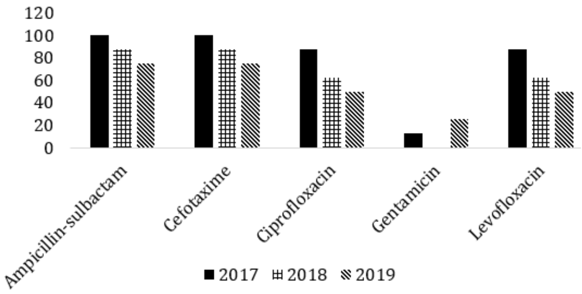

Figure 3. The pattern of antibiotic resistance in *Staphylococcus hominis*

In this study, *S. epidermidis* was highly resistant (more than 60%) to ampicillin-sulbactam and cefotaxime. Ampicillin-sulbactam and cefotaxime can no longer defeat *S. epidermidis* (Figure 1). Antibiotic susceptibility of *S. haemolyticus* fluctuated during the 3 years.

Table III. Logistic regression of DDD versus percentage of antibiotic resistance

Bacteria	p	OR (IK 95%)
Staphylococcus epidermidis	0.403	0.40 (0.0447-3.424)
Staphylococcus haemolyticus	0.311	4.00 (0.273-58.562)
Staphylococcus hominis	0.043	0.063 (0.004-0.915)

In 2019, the bacteria was no longer sensitive to four antibiotics including ampicillin-sulbactam, cefotaxime, ciprofloxacin, and levofloxacin. This condition raises particular concern because levofloxacin is the most used antibiotic during the last 3 years. According to Bhatt *et al*., *S. epidermidis* and *S. haemolyticus* were found to be resistant to penicillin, 30% were resistant to gentamicin, 53% were resistant to ciprofloxacin, and 49% were resistant to levofloxacin (Figure 2). Looking at the more detailed data, three CoNS species in this study had a high percentage of resistance (more than 60%) to Ampicillin-sulbactam and cefotaxime (Bhatt *et al*., 2016). Based on a meta-analysis of the prevalence and antimicrobial resistance of CoNS, the resistance of CoNs to ampicillin, ciprofloxacin, gentamicin, and levofloxacin was 64%, 20%, 27%, and 14%, respectively. The study revealed that CoNS resistance to commonly available antibiotics was high, ranging from 11% to 64% in Ethiopia (Deyno *et al*., 2018).

Additionally, in this study, *S. hominis* susceptibility to four antibiotics increased over 3 years (Figure 3). The antibiotic resistance percentage of this isolate decreased gradually, especially in ampicillin-sulbactam, cefotaxime, ciprofloxacin, and levofloxacin. *S.* hominis isolate was sensitive to gentamycin; however, in 2019, the percentage of antibiotic resistance rose to 25%. There have been limited studies on antibiotic-resistant *S. hominis*. Chaves *et al*. study in 2005, found that 100% of isolates were resistant to penicillin and 23.8% of isolates were resistant to ciprofloxacin (Chaves *et al*., 2005). According to the Mendoza-Olazara´n, 70% of isolates were resistant to ampicillin (Mendoza-Olazarán *et al*., 2013).

Interestingly, in our study, *S. haemolyticus* and *S. hominis* have an emerging profile as multidrug-resistant bacteria. These isolates were resistant to three groups of antibiotics: penicillin, cephalosporin, and quinolone. MDR bacteria lead to increased hospitalization costs, morbidity, and mortality rates (Azimi *et al*., 2019). CDC defined multidrug-resistant bacteria as those that are non-susceptible to at least one antibiotic in three or more drug classes. The relationship between DDD and antibiotic resistance *S. hominis* species (OR = 0.063; CI [0.004-0.915]; p=0.043) (Table III). Antibiotic resistance is caused by multi-factors, for instance, irrational use of antibiotics and the presence of resistant genes circulating in the hospital (Deyno *et al*., 2018; Olivas, 2018; Sanjaya, *et al*., 2012). There was no study assessing the correlation between antibiotic consumption and antibiotic resistance in CoNS infection. However, a meta-analysis study has found that antibiotic consumption was significantly correlated to antibiotic resistance in other bacteria (OR = 2.33; CI [2.91-2.49]; p<0.01). Although several studies found antibiotic consumption was significantly correlated to antibiotic resistance, all of the correlation coefficients were weak (r<0.5) (Bell, Schellevis, Stobberingh, Goossens, & Pringle, 2014)

A resistance can occur among bacteria through the production of "resistance plasmids," pieces of DNA that are capable of being transferred from one bacterial cell to another. The resistance mechanism occurs through three mechanisms that are mediated by plasmids, namely by decreasing membrane permeability (porin), changing receptors on ribosomes, and hydrolysis by esterase (Setiabudi, 2012). In addition, for CoNS species, other mechanisms of resistance include biofilm formation and mutations in the grlA, gyrA, or ParC genes (Mendoza-Olazarán *et al*., 2015). The production of BioFilm by CoNS bacteria is due to unfavorable bacterial environmental conditions, and thus the bacteria make protection using bacterial polysaccharides which are excreted by exopolysaccharides which are covered by extracellular polymers produced by bacteria. In *S.* epidermidis (SE) strains that are resistant to methicillin, mecA gene expression is used as a marker for molecular detection using PCR (Contreras *et al.,* 2013).

This study contributes to providing information about antibiotic resistance patterns for CoNS to be used as an early detection tool for irrationality in antibiotic use and as a source of information in controlling antibiotic resistance. Overall, based on this three years ecological study, ampicillin-sulbactam, cefotaxime, ciprofloxacin, gentamycin, and levofloxacin should not be used to treat CoNS infection. Further study is needed to explore CoNS susceptibility to other antibiotic classes. Moreover, this ecological study using DDD data for antibiotic consumption did not accurately reflect actual antibiotic consumption by individuals at this hospital. Moreover, the ecological study identified antibiotic consumption at the group level, not at the individual level who was infected by the resistant bacteria.

CONCLUSION

The most used antibiotic during 3 years period was levofloxacin. This study also found that 2 out of 3 CoNS species were MDR species which were resistant to ampicillin-sulbactam, cefotaxime, and ciprofloxacin. There was no significant correlation between antibiotic consumption (DDD) with the percentage of antibiotic resistance in three CoNS species. However, this research found there was an inverse relationship between DDD and antibiotic resistance of *S. hominis* species. Further research is needed to identify antibiotic resistance correlation with antibiotic consumption based on the quality of antibiotic prescription.

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