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ANTIBIOTIC CONSUMPTION AND ANTIBIOTIC RESISTANCE PATTERN OF 3 SPESIES COAGULASE NEGATIVE STAPHYLOCOCCI: AN ECOLOGICAL STUDY

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ABSTRACT

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

Key words: antibiotic consumption, antibiotic resistance, ecological study, CoNS

INTRODUCTION

A group of coagulase-negative staphylococci (CoNS) was historically classified as non-pathogenic bacteria. Over the last view decades, the widespread use of implants and increasing the 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 patients 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 *Staphylococcus aureus*, lead to limited therapeutic options (Becker, 2014). *Staphylococcus epidermidis, Staphylococcus hominis and Staphylococcus haemolyticus* are the most common CoNS species infection (Heilmann, Ziebuhr, & Becker, 2019).

In this context, CoNS are playing a primary role as the important group of gram-positive coccoid bacteria that can lead to increased mortality. In recent years, reports of CoNS infection induced bacteraemia, septicaemia, endophthalmitis, and endocarditis have increased rapidly (Bhatt et al., 2016; Von Eiff, Arciola, Montanaro, Becker, & Campoccia, 2006). The prevalence of septicaemia in Indonesia does not have accurate data it ranged from 15 to 37,2%, with a mortality rate of 37-80% caused by septic shock. In Indonesia, especially Bali in regional public hospital, the most common bacteria causing septicaemia are CoNS such as *Staphylococcus haemolyticus, Staphylococcus hominis, and Staphylococcus epidermidis* (Mahendra, Tirtodiharjo, & D Kusuma, 2016; Wahyuni, Nurahmi, 2016). Because of the high prevalence and mortality rate of CoNS, accurate species identification and determination of the antibiotic resistance, profile is important to treat 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 identify the relationship between the use of antibiotic agent for CoNS in Bali's regional public hospital and the development of antibiotic resistance during 3 years period.

Until know, there were a limited study about correlation ship of antibiotic use and antibiotic resistance for CoNS, especially in Bali. Information about antibiotic resistance patterns for CoNS can be used as an early detection tool for irrationality 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 regional public hospital in Bali, Indonesia with 588 beds 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. It was conducted over a three years period (January 1st, 2017 to December 31th 2019) inpatient data. An Institutional Review Board (IRB) exemption application was submitted for this study in May of 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 of 2020.

Antimicrobial resistance data.

Data on susceptibility of CoNS to antibiotics were obtained from the hospital antibiogram of all isolates from 2017 to 2019. Sensitivity results in antibiogram were based on the standards provided by the Clinical and Laboratory Standards Institute (CLSI) with disk diffusion method. Susceptibility results consisted for susceptible to antibiotics (S), intermediately resistant (I), and resistant (R). In our study, intermediate-susceptible and resistant strains were considered resistant. Resistant was expressed as a percentage of those strains among all isolated strains. In addition, multi-drug resistance was defined as 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 was extracted from the electronic pharmacy records at regional public hospital. Use of antibiotics in DDDs/100 bed-days was calculated for each year using the ATC/DDD index and thus hospital utilization was expressed as the number of DDDs/100 bed-days. Consumption data was shown as drug utilization 90% (DU90%) profiles for three years periods. DU90% can be used to analyses the quality of drug prescribing and analyses 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 on bacterial resistance to the drugs.

Statistical analysis.

DDDs/100 bed-days of antibiotics from 2017 to 2019, was presented as number of doses. For each antibiotics, 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 identified by DU90% method.

The association between percentage of resistant and the three consecutive study years, 2017 to 2019, were analyzed using descriptive statistics.

Finally the relationships between DDDs/100 bed-days of each antibiotics and rates of antibiotic resistance of each resistant strains of CoNS were tested using Spearman rank correlation and logistic regression. All correlation tests were conducted using a significant level set at $P < 0.05$ and Odds Ratio (OR) with 95% CI. All analyses were performed using Statistical Process for Social Sciences (SPSS) software (Version 22.0 SPSS IBM, USA)

RESULT AND DISCUSSION

Antibiotic consumption data for 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. According to table 1, there were seven antibiotics that included to DU90%. These antibiotics belong to beta lactam group, quinolone and aminoglycoside group. Both The most antibiotics used in the hospital based on DDD parameter during 3 years period was Levofloxacin. DDD levofloxacin and cefotaxime rose during 3 years. On the other hand ampicillin-sulbactam use was drop slightly during the period.

Data from 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 those reported from our study results that cephalosporins and quinolones were the most widely used antibiotics during 2017-2018. Until this now, there is not available report about antibiotic consumption during 2019 by WHO in South-East Asia (World Health Organization, 2018). The study at GSL General Hospital, India, for a period of one month, November 2019 found that the most frequently used antibiotics class were penicillin, third-generation cephalosporins, and quinolones. In this study study the rate of utilization of antibiotics was found to be 78% (Kumar, Krishna, P Sindusha, & M Susritha, 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 four out of the 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 distribution data about DU90% of antibiotics in our study. Levofloxacin, ceftriaxone, Ampicilin, Cefotaxime, Ciprofloxacin, Ampicillin-sulbactam, and Gentamicin were included in the DU90% segment list.

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

The graph in Figure 1-3 show the pattern of percentage resistance CoNS to Ampicilin-Sulbactam, Cefotaxime, Ciprofloxacin, Gentamicin, and Levofloxacin at regional public hospital in Bali during 2017-2019. Three CoNS species that had observed were *Staphylococcus epidermidis, Staphylococcus haemolyticus* and *Staphylococcus hominis*, with total 50 isolates. In 2018 there was a decrease in the percentage of antibiotic resistant, but in 2019 there was an increase in resistance again. Based on the result, three type of CoNS have different resistance pattern during 3 years. Different species of CoNS show different susceptibility of antibiotics and resistance pattern (Azimi, Maham, Fallah, Azimi, & Gholinejad, 2019)

In our study, *Staphylococcus epidermidis* was high resistance (more than 60%) to Ampicilin-Sulbactam and Cefotaxime. Ampicillin-sulbactam and Cefotaxime were no longer can defeat *Staphylococcus epidermidis*. Antibiotic susceptibility of *Staphylococcus haemolyticus* were fluctuated during 3 years. In 2019, the bacteria no longer sensitive to four antibiotics involve Ampicillin-sulbactam, cefotaxime, ciprofloxacin and levofloxacin. This condition need particular concerned, because levofloxacin is the most antibiotic used during last 3 years. According to Bhatt et al., *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* were found to be resistant to penicillin, 30% were resistant to gentamicin, 53% were resistant to Ciprofloxacin, and 49% resistant to levofloxacin. Looking in more detail at the data, three CoNS species in this study have a high percentage of resistance (more than 60%) to Ampicillin-sulbactam and cefotaxime (Bhatt et al., 2016). Based on Meta-analysis of prevalence and antimicrobial resistance of CoNS, the resistance CoNs to Ampicilin, Ciprofloxacin, Gentamicin, and Levofloxacin was 64%, 20%, 27%, and 14%. The study revealed that CoNS resistances to commonly available antibiotics were high, ranging from 11% to 64% in Ethiopia (Deyno, Fekadu, & Seyfe, 2018).

Additionally, in our study *Staphylococcus hominis* antibiotic susceptibility to four antibiotics were increase during 3 years. Antibiotic resistance percentage of this isolate were decrease gradually especially in Amphicillin-sulbactam, Cefotaxime, ciprofloxacin, and levofloxacin. Staphylococcus hominis isolate was sensitive to gentamycin, however in 2019 the percentage of antibiotic resistance rose to 25%. There were limited study about antibiotic resistant *Staphylococcus hominis*. Chaves et al. study in 2005 found that 100% isolates were resistant to penicillin and 23.8% isolates were resistant to ciprofloxacin (Chaves, Lvarez, Sanz, And, & Otero, 2005). Acoording the Mendoza-Olazara´n, 70% isolates were resistant to ampicillin (Mendoza-Olazarán et al., 2013).

Interesting finding in our study that *Staphylococcus haemolyticus* and *Staphylococcus hominis* have emerging profile as multidrug-resistant. These isolates were resistant with three group antibiotics involve penicillin, cephalosporin and quinolone. MDR bacteria lead to increase the hospitalization cost, morbidity and mortality rates. Furthermore, MDR bacteria restrict therapeutics choice of antibiotic (Azimi et al., 2019) CDC was defined multidrug-resistant as non-susceptible to at least one antibiotic in three or more drug classes. Based on spearman correlation analysis, in general there was no significant correlation between antibiotic consumption (DDD) with the percentage of antibiotic resistance of three CoNS species ($p>0.05$). However this research found there was an inverse relationship between DDD and antibiotic resistance *Staphylococcus hominis* species (OR = 0.063; CI [0.004-0.915]; $p=0.043$). Antibiotic resistance is caused by multifactorial for instance irrational use of antibiotic and presence of resistant genes that circulating in the hospital (Deyno et al., 2018; Olivas, 2018; Sanjaya, Herawati, & Marjadi, 2012).

Resistant event can occur between individual 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, the mechanism of resiatance is biofilm formation and usually a mutation 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, so the bacteria make a protection from bacterial polysaccharides which are excreted by exopolysaccharides which are covered by extracellular polymers produced by bacteria. In Staphylococcus 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).

The limitation of this ecological study was DDD data for antibiotic consumption not accurately reflect actual antibiotic consumption by individuals at this hospital. Moreover ecological study was identify antibiotic consumption in group level not in the individual level who was infected by the resistant bacteria.

CONCLUSION

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

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TABLE AND FIGURE

Table 1. 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	
ceftriaxone	100.45	107.97	122.42	330.84	21.87	90%
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			

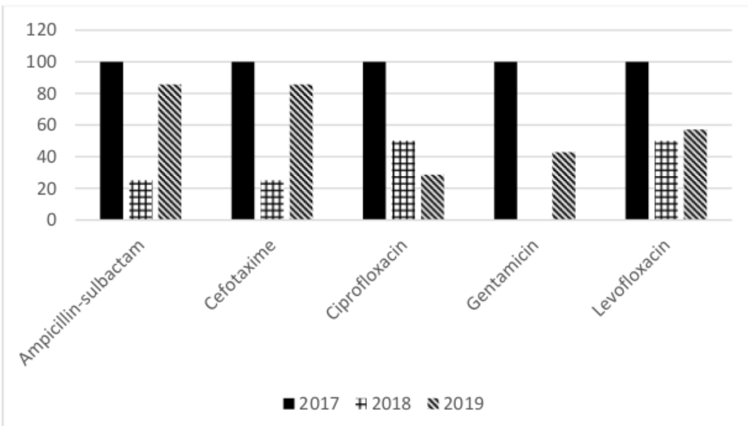

Figure 1. The pattern of antibiotic resistance *Staphylococcus epidermidis*

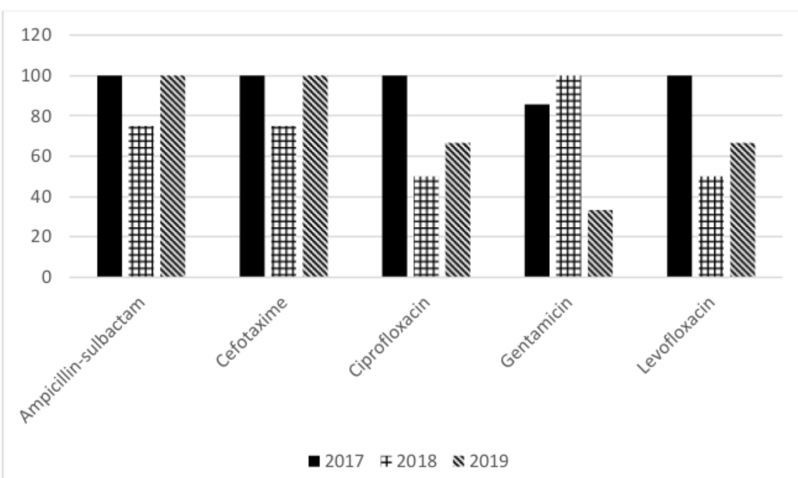

Figure 2. The pattern of antibiotic resistance *Staphylococcus haemolyticus*

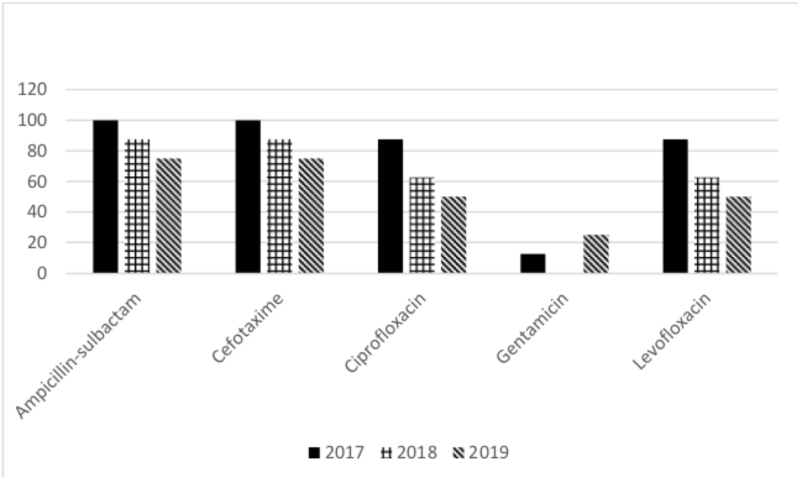

Figure 3. The pattern of antibiotic resistance *Staphylococcus hominis*

Table 2. 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

Table 3. Logistic regression of DDD versus percentage of antibiotic resistance

Bakteri	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)

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