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VANCOMYCIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AT THE DR. WAHIDIN SUDIROHUSODO HOSPITAL MAKASSAR

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ABSTRACT

Vancomycin-Resistant *Staphylococcus aureus* (VRSA) refers to bacteria that have complete resistance to Vancomycin. The increasing prevalence of VRSA can be a significant clinical problem limited therapeutic options. This study aimed to identify the susceptibility of *Staphylococcus aureus* to antibiotic vancomycin and to know the prevalence and characteristics of patients with VRSA at the Dr. Wahidin Sudirohusodo Hospital Makassar. Therefore, the identification of VRSA is necessary to improve the management of antibiotic therapy, infection control and to prevent the occurrence of wider resistance. This retrospective descriptive study used secondary data of antibiotic susceptibility test on *S.aureus* identified using VITEK 2 and patient medical records from January 2015 to December 2016. Of 387 *S.aureus* isolates obtained, 45 (11%) were VRSA. The most common VRSA isolates were male patients (57.8%) with the mean age being 41-60 years old (35.6%). The treatment ward with the most VRSA isolates was from surgical ward (20%), and internal medicine ward (15.6%) whereas the VRSA isolates from the outpatient record was from Surgical Department (8.9%), Dermatology Department and ENT Department (2.2%). The most common specimens were blood (28.9%), pus (26.7%), and sputum (20.0%). The highest prevalence of VRSA was found in patients using ≥ 3 invasive medical devices and 11 (24.4%) of the patients died. Linezolid, Quinupristin/Dalfopristin, Tigecycline, and Nitrofurantoin as a therapeutic option had > 90% sensitivity. Most of VRSA patients were found in the surgical ward. This study emphasizes the need for immediate action by the infection control division, especially in the related units to prevent the transmission.

Key words: *Staphylococcus aureus*, vancomycin, VRSA, Makassar

INTRODUCTION

Development of bacterial resistance is the primary concern in health care. Vancomycin-Resistant *Staphylococcus aureus* (VRSA) is a *Staphylococcus aureus* strain that has been resistant to antibiotic vancomycin. This antibiotic is a drug of choice to treat infections with Methicillin-Resistant *Staphylococcus aureus* (MRSA).[1,2]

Vancomycin is an antibiotic that belongs to glycopeptide group that works by inhibiting synthesis of Gram-positive bacterial cell wall. The inappropriate use and administration of vancomycin may result in the increased occurrence of *S. aureus* resistance to vancomycin.[2,3]

The mechanism of resistance in VRSA strain involves the target change in the vanA gene, resulting in significantly decreased vancomycin binding to target that prevents it from performing its normal functions in inhibiting bacterial cell wall. VanA gene source isolated in VRSA is presumably derived from horizontal gene transfer with Vancomycin-Resistant *Enterococcus* (VRE).[4,5]

VRSA occurrence has increased in various parts of the world. By 2017, more than 30 cases have been reported in Europe, Asia, United States, and Africa. In Indonesia, VRSA had been reported from Purwokerto and Palembang. This finding indicates that the occurrence of this strain is a global issue.[2,3]

Classification of *S.aureus* isolates with reduced susceptibility to vancomycin is based on laboratory breakpoints assigned by Clinical and Laboratory Standards Institute (CLSI). *Staphylococcus aureus* strain is termed as Vancomycin-Resistant *Staphylococcus aureus* (VRSA) at Minimum Inhibitory Concentration (MIC) ≥ 16μg/mL, Vancomycin Intermediate *Staphylococcus aureus* (VISA) at MIC between 4-8μg/mL and Vancomycin Susceptible *Staphylococcus aureus* (VSSA) at MIC ≤ 2 μg/mL.[6]

The increased prevalence of VRSA is a significant factor affecting the nosocomial infection because *Staphylococcus aureus* is the most pathogenic bacteria causing infections acquired in the hospital.

This phenomenon can be a significant clinical problem because infection treatment will become more difficult with limited therapeutic options. Therefore, identification of VRSA is necessary to control infection and to prevent the resistance from spreading.[1,5] This study aimed to identify the susceptibility of *Staphylococcus aureus* to antibiotic vancomycin and to know the prevalence and characteristics of patients with VRSA at the Dr. Wahidin Sudirohusodo Hospital Makassar.

METHODS

This study was a retrospective descriptive study. Data were obtained from Tropical and Infectious Diseases sub-unit of Clinical Pathology Laboratory and Medical Record Installation of the Dr. Wahidin Sudirohusodo Hospital Makassar. Study samples were secondary data from antibiotic susceptibility test results in *Staphylococcus aureus* identified using VITEK 2 and from patients medical records from January 2015 to December 2016. The secondary data that were obtained from the Clinical Pathology Laboratory consisted of patient identity, specimen type, care unit, and antibiotic susceptibility test. The next data were diagnosis, management, output status, health equipment use (catheter, infusion set, ventilator, CVC), and risk factors to VRSA which were obtained from medical record data. The data were inputted using SPSS and results will be displayed in tables and graphs. Ethical clearance was obtained from the Medical Research Ethics Commission, Faculty of Medicine, Hasanuddin University/Dr. Wahidin Sudirohusodo Hospital, Makassar with number 463/H4.8.4.5.31/PP36-KOMETIK/2017.

RESULTS AND DISCUSSION

From January 2015 to December 2016, data from 387 *S.aureus* isolates were obtained. According to these data, the highest frequency of *S.aureus* was observed in June 2016 (26 isolates), whereas the lowest rate of S. aureus was found in May 2015 and July 2015 (7 isolates).

Table 1. The pattern of *Staphylococcus aureus* susceptibility to vancomycin

Category of susceptibility	Frequency (n)	Percentage (%)
Resistant	45	11
Intermediate	11	2
Sensitive	331	85
Total	387	100

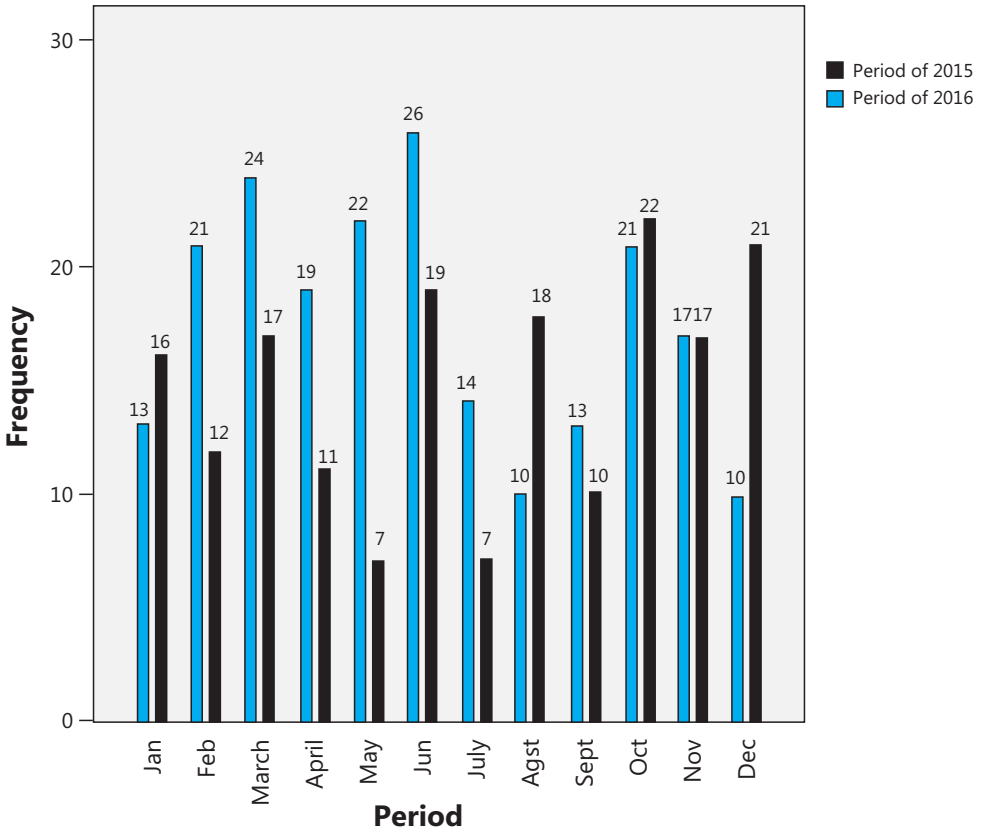

Figure 1. Distribution of *Staphylococcus aureus* isolates frequency from January 2015 to December 2016

Table 2. Distribution of VRSA isolates in a clinical specimen

Clinical Specimen	Frequency (n)	Percentage (%)
Body fluids (transudates/exudate)	3	6.7
Blood	13	28.9
Pus	12	26.7
Sputum	9	20.0
Urine	1	2.2
Tissue	7	15.6
Total	45	100

All the identified *S.aureus* isolates were tested for vancomycin susceptibility. The testing results showed VRSA (11%), VISA (2%) and VSSA (85%).

This study results indicated that the prevalence of VRSA in the Dr. Wahidin Sudirohusodo Hospital Makassar was 11%. Another study in Indonesia during 2010 in Margono Soekarjo Hospital Purwokerto found that the prevalence of VRSA was 15.6% from the stethoscope membrane. Whereas a study in the Dr. Mohammad Hoesin Hospital Palembang from October 2012 to September 2013 reported 1.7% prevalence for VRSA. A study by Moses *et al*. in Nigeria found 5.3 prevalence for VRSA, whereas a study by Thati *et al*. in India reported 1.9% prevalence for VRSA. These findings indicate that VRSA prevalence in Indonesia is higher compared to other countries and it needs a serious attention.[2,3,7]

Table3. Characteristics of the samples

Variable	VRSA n (%)
Sex	
Male	26 (57.8)
Female	19 (42.2)
Age (years)	
≤18	9 (20)
19 – 40	14 (31.1)
41 -60	16 (35.6)
> 60	6 (13.3)
Number of health device	
0 – 1	10 (22.2)
2	7(15.6)
≥3	28 (62.2)
Clinical outcome	
Cured	5 (11.1%)
Improved	29 (64.4%)
Died	11 (24.4%)

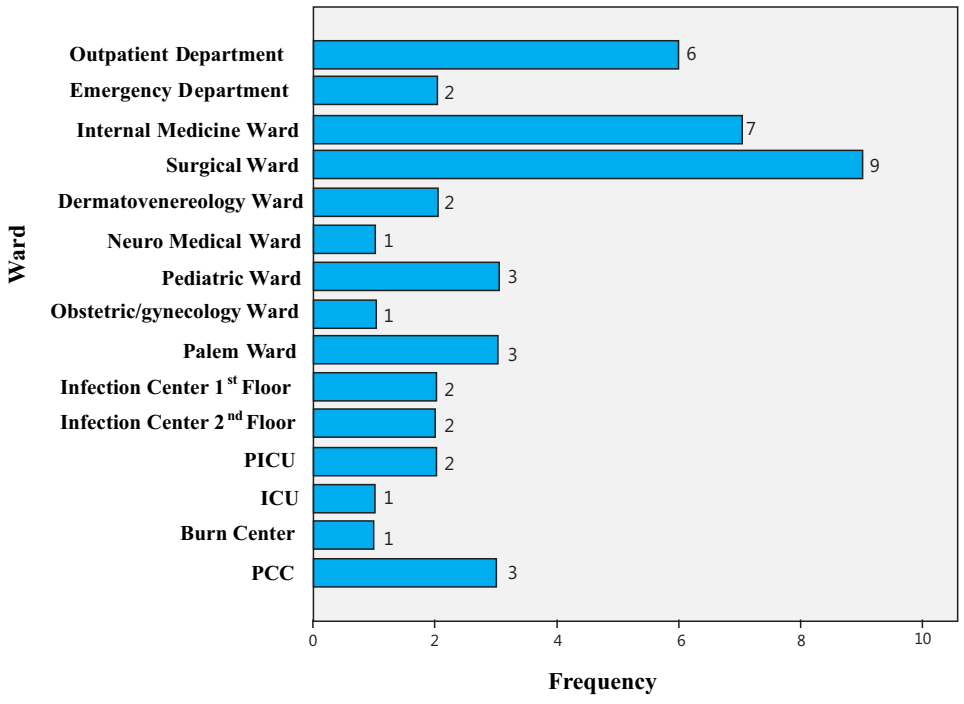

Figure 2. Prevalence of VRSA according to the treatment unit

The increased VRSA spreading can be caused by several risk factors such as length of stay in hospital, history of surgery, the use of invasive health device, patients with chronic illness (e.g. diabetes, renal diseases), history of previous infections with MRSA or VRE, and previous exposure to vancomycin (particularly in recurrent or prolonged cases).[8,9]

VRSA isolates were obtained from various clinical specimens including body fluids (transudates/ exudates), blood, pus, sputum, urine, and tissues. The most prevalent VRSA was found in a blood specimen (13, 28.9%), pus (12, 26.7%), and sputum (20%). Similar results were reported from a study by Saadat *et al*. which found that the most prevalent VRSA was in blood and pus specimen.[4,5,7]

Data were also grouped according to several variables. The highest VRSA isolate number were from male patients (57.8%) and the mean age of 41-60 years old (35.6%). According to the number of health devices used (infusion set, urine catheter, ventilator and Central Venous Catheter (CVC)), the highest VRSA prevalence was observed in the use of n ≥3 invasive health devices (57.8%). This finding was in accordance with the risk factor of VRSA infection, namely the use of invasive health devices can make a patient vulnerable to VRSA infection. Whereas by clinical outcome of 29 patients (64.4%) were improved after treatment and 11 (24.4%) died.

The total number of VRSA isolates from inpatients were 381 isolates, whereas from outpatients were six isolates. Treatment unit with highest VRSA isolates was surgery unit (20%), and internal unit (15.6%), whereas VRSA isolates from outpatients were derived from Surgery Outpatients (8.9%), Dermatovenereology Outpatients, and Rhinology Outpatients (2.2%). These findings indicated that the high prevalence of VRSA particularly in Surgery Unit (Ward, Outpatients or Emergency Department). These results were following a study by Mahmudah *et al*. found that surgical wound infections due to bacteria in Indonesia can occur in Surgery Care Unit. Whereas the low prevalence in other care units (e.g., ICU, PICU, infection center 2nd floor) is probably related to proper infection control.

This study also evaluated other characteristics such as diagnosis, comorbidity factors, and risk

Table 4. Characteristics of samples

Variable	VRSA n (%)
Diagnosis	
Infection diseases	4 (8.9)
Neoplasm	7 (15.6)
Hematological diseases	2 (4.4)
Endocrine, metabolic and nutritional	2 (4.4)
Nervous system diseases	5 (11.1)
Otorhinolaryngology diseases	1 (2.2)
Cardiovascular system diseases	1 (2.2)
Respiration system diseases	4 (8.9)
Gastrointestinal system diseases	1 (2.2)
Cutaneous and subcutaneous tissues	3 (6.7)
Musculoskeletal system diseases	8 (17.8)
Urogenital system diseases	7 (15.6)
Risk factors	
Hospitalization history	29 (64.4)
Hemodialysis measure	5 (11.1)
Surgery measure	10 (22.2)
Chronic diseases	
Renal diseases	8 (17.8)
Diabetes melitus	8 (17.8)

Table 5. The results of VRSA susceptibility test to antimicrobial

Antibiotic	Resistant n (%)	Intermediate n (%)	Sensitive n (%)
Benzylpenicillin	42 (93.3)	0	3 (6.7)
Oxacilin	24 (53.3)	0	21 (46.7)
Gentamicin	6 (13.3)	0	39 (86.7)
Ciprofloxacin	13 (28.9)	1(2.2)	31 (68.9)
Levofloxacin	13 (28.9)	0	32 (71.1)
Moxifloxacin	8 (17.8)	5 (11.1)	32 (71.1)
Erytromicin	11 (24.4)	1 (2.2)	33 (73.3)
Clindamycin	13 (28.9)	1 (2.2)	31 (68.9)
Quinupristin/Dalfopristin	2 (4.4)	0	43 (95.6)
Linezolid	3(6.7)	0	41 (91.1)
Tetracycline	24 (53.3)	0	21 (46.7)
Nitrofurantoin	0	0	45 (100)
Rifampicin	5 (11.1)	2 (4.4)	38 (84.4)
Trimetoprim/ Sulfamethoxazole	5(11.1)	0	40 (88.9)
Tigecyline	0	0	45(100)

factors (in the last three months) to VRSA. According to diagnosis, the highest VRSA isolates were found in patients with musculoskeletal system diseases (17.8%), urogenital system diseases and neoplasm (15.6%). The data also indicated that chronic diseases contribute to risk factors of VRSA were diabetes mellitus and renal diseases (17.8%). These findings were consistent with cases reported by Finks *et al*. where each patient had a substantial concurrent condition that contributed to their disease.[1]

Susceptibility test for VRSA to antibiotics indicated that the antibiotic remained sensitive >90% was Tigecycline (100%), Quinupristin (95.6%) and Linezolid (91.1%). The resistance of >50% was obtained with antibiotic Benzylpenicillin (93.3%), Oxacillin(53.3%), and Tetracycline (53.3%).

In this study, the number of VRSA resistant to Quinupristin/Dalfopristin were 2 (4.4%) and 3 (6.7%) for Linezolid and Quinupristin-Dalfopristin. This result was in accordance with the results of a study by Saadat *et al*. which found VRSA resistant to Linezolid and Quinupristin-Dalfopristin.[7]

The limitation of this study was the lack of data supporting the VRSA risk factors such as treatment history in other hospitals, history of exposure to antibiotic vancomycin, and history of infection with MRSA or VRE.

CONCLUSION AND SUGGESTION

In the present study, the number of VRSA identified in the Dr. Wahidin Sudirohusodo Hospital was 11%. This finding has an important implication for the therapeutic dilemma caused by the existence of multi-resistant organisms in recent years.

According to this study findings, it is suggested to prevent the spreading and occurrence of resistance to glycopeptide by early detection of resistant strains, screening the patients with high risks to VRSA, antibiotic use at the national level and adopt appropriate infection control measures to reduce the incidence of nosocomial infections in the hospital.

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