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Methicillin-Resistant Staphylococcus aureus (MRSA) Patterns and Antibiotic Susceptibility in Surgical and Non-Surgical Patients in a Tertiary Hospital in Indonesia

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Abstract

Methicillin-Resistant Staphylococcus aureus (MRSA) in the hospital is found mainly in surgical patients, which increases morbidity and mortality. Currently, vancomycin is the drug of choice for the treatment of MRSA infections. The increasing use of vancomycin and its inappropriate administration may increase the resistance of *S. aureus* to vancomycin. This study aimed to describe the distribution of MRSA and types of antibiotics that are still sensitive to MRSA in surgical and non-surgical patients. This cross-sectional, observational, retrospective descriptive study was conducted at the Microbiology Laboratory, Dr. Hasan Sadikin General Hospital, in 2019 using secondary data on the results of culture examination and antibiotic susceptibility of positive S. aureus culture isolates from all types of isolates from surgical and non-surgical patients. All specimens were cultured in appropriate media. Identification of S. aureus was performed by Gram staining to identify bacterial morphology, and automatic tools. Antibiotic susceptibility test was performed using an automatic machine. Seventy-five isolates (17%) were identified to be MRSA with 46 (53%) of them retrieved from surgical patients. Most of the MRSA isolates came from pus and were mostly due to skin infections. Antibiotic susceptibility results showed two *Vancomycin-Resistant Staphylococcus aureus* (VRSA) isolates from surgical patients. The positive culture of the MRSA and VRSA was dominated by surgical patients with pus coming from surgical wound infection, burn, and other skin infection as the most common sources. Thus, the proportion of MRSA isolates in the hospital in 2019 is 17% and two VRSA isolates are identified in the same year. The surgical ward was the primary origin of most MRSA isolates. Further studies are necessary to identify the MRSA incidence rate, evaluation and periodic monitoring of antibiotic use, and active surveillance in the surgical patient rooms.

Keywords: Antibiotic susceptibility, MRSA, surgical patients, VRSA

Pola Bakteri *Methicillin-Resistant Staphylococcus aureus* (MRSA) dan Kepekaan Antibiotik pada Pasien Bedah dan Non Bedah di Rumah Sakit Tersier Indonesia

Abstrak

Keberadaan *Methicillin-Resistant Staphylococcus aureus* (MRSA) di rumah sakit banyak ditemukan terutama pasien bedah yang meningkatkan morbiditas dan mortalitas. Saat ini *vancomycin* adalah *drug of choice* untuk terapi infeksi MRSA. Peningkatan penggunaan *vancomycin* dan pemberiannya yang tidak tepat memungkinkan terjadinya peningkatan resistensi *S. aureus* terhadap *vancomycin*. Oleh karena itu, penelitian ini bertujuan mengetahui gambaran sebaran bakteri MRSA dan jenis antibiotik yang masih sensitif terhadap MRSA pada pasien bedah dan non bedah. Penelitian potong lintang, observasional, deskriptif retrospektif ini dilakukan di Laboratorium Mikrobiologi Rumah Sakit Dr. Hasan Sadikin (RSHS) pada tahun 2019 dengan data sekunder hasil pemeriksaan biakan dan resistensi antibiotik isolat kultur positif *S. aureus* dari semua jenis isolat dari pasien bedah dan non bedah. Semua spesimen akan dikultur lalu identifikasi *S.aureus* dengan melakukan pewarnaan Gram, melihat morfologi bakteri, dan alat otomatis. Uji kepekaan antibiotik menggunakan mesin otomatis. Tujuh puluh lima (17%) isolat merupakan MRSA dan 46 (53%) di antaranya berasal dari pasien bedah. Hasil kepekaan antibiotik menunjukkan 2 isolat *Vancomycin-Resistant Staphylococcus aureus* (VRSA) yang berasal dari pasien bedah. Hasil kultur positif MRSA dan VRSA didominasi oleh pasien bedah dengan sumber tersering isolat pus yang berasal dari luka *surgical site infection,* luka bakar, dan infeksi kulit lainnya. Pada tahun 2019 jumlah isolat MRSA 17%, dua di antaranya merupakan isolat VRSA. Bangsal bedah merupakan ruangan asal isolat MRSA terbanyak. Disarankan penelitian lebih lanjut mengenai angka kejadian MRSA, evaluasi dan pemantauan penggunaan antibiotika secara berkala, identifikasi dan *surveillance* aktif di ruangan pasien bedah.

Kata kunci: Kepekaan antibiotik, MRSA, pasien bedah, VRSA

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Introduction

Methicillin-resistant Staphylococcus aureus or MRSA is a *Staphylococcus aureus* (*S. aureus*) strain that is resistant to *isoxazoyl penicillins*, such as flucloxacillin, methicillin, oxacillin, and cefoxitin, which are still the world's leading nosocomial pathogenic bacteria. *Methicillin-resistant Staphylococcus aureus* is also cross-resistant to all beta-lactam antibiotics.[1,2]

Severe infections due to MRSA have created a new challenge for health practitioners due to increased risk of morbidity and mortality, as well as a tendency to increase the frequency of MRSA in various countries. In The United States found more than 50% of *S. aureus* specimens in intensive care were MRSA.[3,4] To date, MRSA data in Indonesia is very limited. The prevalence of MRSA in Dr. Soetomo Hospital Surabaya in 2016 was 8.2% of 643 patients in 3 months.[5] In 2010, a research was conducted at Dr. Wahidin Sudirohusodo, Makassar, Indonesia that of the total MRSA specimens, the incidence of 51.9% was observed in surgical patients (44.4% in post-surgery and 7.5% in diabetic foot care) f.[6] The number of positive specimens for MRSA in Dr. Hasan Sadikin General Hospital Bandung (RSHS) in 2018 was 22(11.16%) of 197 positive *S. aureus* specimens. From the results of several MRSA studies, it is apparent that there is an increasing number of MRSA from year to year. Despite a low prevalence of MRSA in Indonesia when compared to other countries, it is still necessary to apply a countermeasure strategy to prevent further infection.[7]

Methicillin-resistant Staphylococcus aureus is typically classified as hospital acquired, health care acquired. Hospital-acquired MRSA is usually seen in nosocomial infection, which is often acquired after a surgical or invasive medical procedure during a hospital stay. The main transmission of MRSA is through patient-to-patient contact, possible contamination through unwashed hands of medical staff and nurses, airborne transmission from patients with MRSA pneumonia or those using air conditioners (ventilators). MRSA infection usually worsens the patient's condition. The higher the number of patients infected with MRSA in the hospital is, the higher the danger of infection/transmission of MRSA. MRSA infection can cause lethal bacteremia (fatal), endocarditis, and pneumonia, especially in critically ill patient.[3,4]

Currently, vancomycin is the drug of choice for the treatment of MRSA infections. The increasing use of vancomycin and its inappropriate administration to treat infections caused by MRSA may increase the resistance of *S. aureus* to vancomycin. *Vancomycin-Resistant Staphylococcus aureus* (VRSA) refers to bacteria that have resistance to *vancomycin*. Several studies have demonstrated that MRSA and VRSA are widely found in the hospital environment, especially among surgical patients. The Centers for Disease Control and Prevention (CDC) suggests that the risk factors for MRSA and VRSA infections are individuals who have been hospitalized or undergoing surgery in the past year, have permanent medical aids in their bodies, and reside in long-term care facilities.[8-10]

Due to the importance of preventing and treating MRSA infections, this study aimed to describe the distribution of MRSA bacteria to be used as a basis for evaluating and monitoring the incidence of MRSA and sensitive antibiotics for treating the infection in surgical and non-surgical patients in Dr. Hasan Sadikit General Hospital, Bandung, Indonesia.

Methods

This study was a retrospective observational descriptive study conducted at the Microbiology Laboratory of the Clinical Pathology Department, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia in 2019. Data were collected in a cross-sectional manner. This study used secondary data on results of culture and antibiotic resistance examinations with *S. aureus* positive culture specimens from surgical and non-surgical patients sent to the Microbiology Laboratory of the Clinical Pathology Department of the hospital during the period of 2019. Data collected were patients' age and sex, specimen type, and origin of the specimen. Data were processed using Microsoft Excel and presented descriptively.

For each specimen, culture examination and antiobiotic resistance testing were performed as follows: All specimens were cultured in an appropriate media (blood agar) and growth was identified after 24 hours. The identification of *S. aureus* was done by performing Gram staining and examining the bacterial morphology, as well as performing identification using automatic tools. Bacterial susceptibility test method was performed using an automatic machine (Vitek-2 compact), which results in identification of the susceptibility to antibiotics that have been validated according to the international standards (CLSI=Clinical Laboratory Standard

International). Three stages of inspection was performed using this instrument: preparation and standardization of inoculum turbidity; data entry using a barcode system; and inserting a card into the instrument. Afterwards, the process of inoculation, incubation, reading, validation and result interpretation was carried out automatically by the tool.

The inclusion criteria for the subjects of this study are positive culture specimens from all types of specimens sent to the Microbiology Laboratory of the hospital in 2019 period with complete data, including data on age, sex, type of specimen, origin of specimen, and data on antibiotic susceptibility. The exclusion criteria for the subjects of this study were the results of MRSA-positive isolates from outside the study hospital. The percentage of MRSA was expressed by the number of MRSA samples compared to all *S. aureus* positive culture specimens during the study year. This study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia number: LB.02.01/X.6.5/70/2020.

Result

In 2019, 467 *S. aureus* specimens were sent to the Microbiology Laboratory of the hospital. Department. The distribution of the specimens is depicted in Figure 1.

During 2019, a total of 18,914 isolates were obtained from 17,318 patients. Total positive cultures were seen in 9,969 (52.31%) isolates from 9,059 patients. Of these positive cultures, 467 (4.68%) isolates were identified as growing *S. aureus* and 75 of them were identified as MRSA positive (17%). These came from 72 patients, 31 female patients and 41 male patients. Three patients with MRSA positive specimens had specimens collected from different places. These three patients were one baby boy and two adult patients. Based on age, the incidence of MRSA infection was more common in adulthood, with 67 people (93%) compared to 5 children (7%). The MRSA Sample Characteristics Data are presented in Table 1.

Specimens with MRSA positive results were collected from surgical and non-surgical patients from the inpatient rooms, outpatient clinics, and emergency services of the hospital. From 75 MRSA specimens, 46 specimens came from surgical patients, and 29 specimens came from non-surgical patients. The forty-six specimens from surgical patients were obtained from surgical inpatient rooms (n=24), surgical emergency room (n=11), and surgical, orthopedic, urology, and ENT clinics (n=11). The remaining 29 specimens came from non-surgical patients, with 24 came from non-surgical inpatient rooms, 2 from non-surgical emergencies, and 3 from non-surgical outpatient clinics. The Emergency Room was the site with the highest number of MRSA specimens (n=13, 17%). The distribution of MRSA by collection site is presented in Figure 2.

The MRSA specimens collected consisted of pus (40 specimens), blood (9 specimens), sputum (16 specimens), urine (7 specimens),

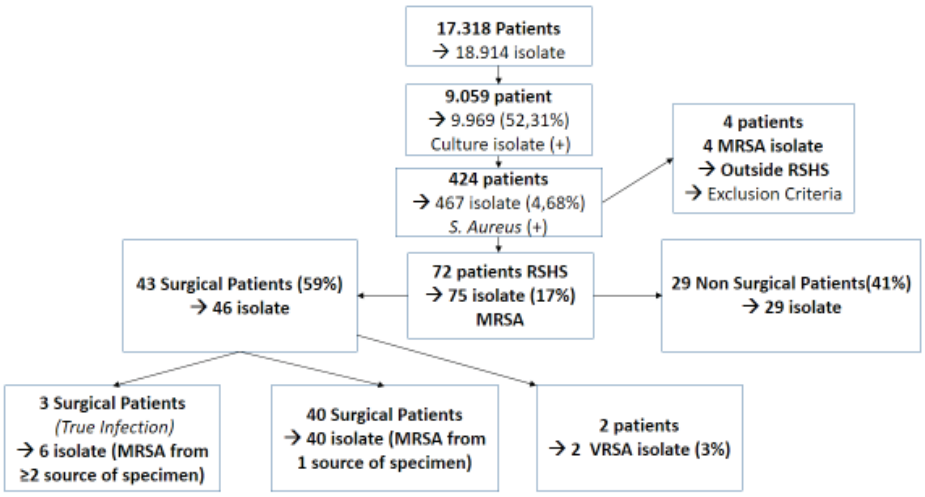

Figure 1 MRSA Identification Results

Table 1 MRSA Sample Characteristics

Characteristics	Total	(%)
Age (years)		
Adult	67	93
Child	5	7
Gender		
Men	41	57
Women	31	43

CSF (2 specimens), and body fluids (1 specimen), as depictedn in Figure 3.

An antibiotic susceptibility test was performed on these specimens after the identification of the MRSA. The antibiotics of choice for MRSA are vancomycin, linezolid and tigecycline. The antibiotic susceptibility results showed that 73 (97%) isolates were sensitive to vancomycin, while the remaining 2 were resistant to this antibiotics. The vancomycin resistant isolates were from surgical inpatients. All isolates were sensitive to linezolid and tigecycline. Further details of this antibiotic susceptibility test results are listed in Table 2.

Discussion

Methicillin-Resistant Staphylococcus aureus is a globally important nosocomial pathogen and the increased frequency of MRSA infection in the community will increase morbidity and mortality. The global antimicrobial resistance surveillance system (GLASS) report published by WHO in 2018 described a study on 1,530 positive cultures from bacteremia patients in Thailand, stating that 149 (9.7%) were positive for *S. aureus,* with 28 (19%) were positive for MRSA.[10-12]

In this present study, 9,969 positive culture specimens were identified during the period

Table 2 Isolates Distribution by Antibiotic Susceptibility

	Surgical Patient (n=46)		Non-Surgical Patient (n=29)	
	nS	%S	nS	%S
Linezolid	46	100	29	100
Tigecycline	46	100	29	100
Vancomycin	44	97	29	100

nS = number of isolate ; S= susceptibility

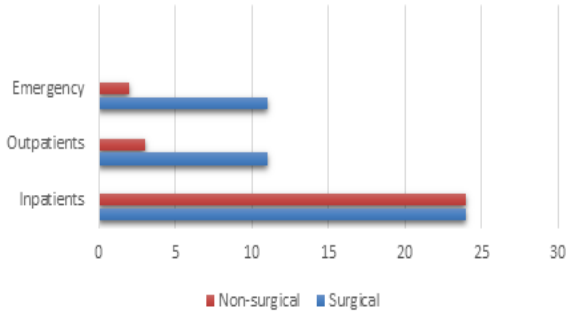

Figure 2 Distribution of MRSA by Collection Site

of 2019, which was 52.31% from the total of 18,914 specimens. This study focused on 467 (4.68%) samples *S. aureus* positive cultures. It was identified that 75 (17.56%) of these samples were MRSA Gram-positive cultures. When compared to data from GLASS report (WHO, 2018), the incidence of MRSA in Dr. Hasan Sadikit General Hospital was lower. The number of specimens positive for MRSA in this hospital in 2018 was 22 (11.16%) of 197 *S. aureus* positive specimens. Several recent MRSA studies also stated that there has been an increasing number of MRSA from year to year, requiring good countermeasures to be applied to prevent further infections.[10]

The 75 MRSA positive cultures identified in this study were obtained from 72 patients, with three of them had specimens from different collection stite. These three patients fall into the true infection category since one of the criteria for true infection is the discovery of the same organism in cultures from different specimens take from different sites.[13]

The three patients who experienced the true infection were a baby boy and two adults. The

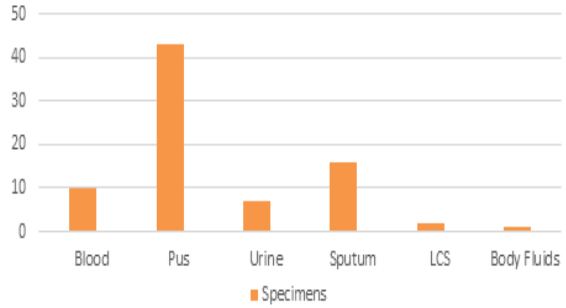

Figure 3 Distribution of Types of Specimens with MRSA Positive Result

first patient was a one-month-old baby boy diagnosed with hydrocephalus and secondary infection in postoperative wounds who was hospitalized in the surgical inpatient room. The MRSA positive results in this baby were obtained in pus culture from the head, cerebrospinal fluid culture, and body fluid culture from VP shunt, and CSF culture. This is in accordance with one of the risk factors for MRSA, namely the use of invasive medical devices. The second patient with true infection was a 28-year-old woman with a diagnosis of combustio and diabetes mellitus treated in a surgical inpatient room. In this patient, positive MRSA results were obtained in the pus and blood cultures. This is in accordance with one of the risk factors for MRSA, namely the length of stay in the hospital and previous chronic disease. The third patient, a 28-year-old male with a diagnosis of *p*emphigus vulgaris and abcess at the frontal region, was an outpatient surgery positive patients with positive MRSA results obtained from pus cultures from the forehead and scalp. This third patient has a history of being treated for approximately 1 month at the nearest health center near his house. The three patients included in the criteria for true infection were surgical patients and the majority of MRSA-positive specimens were pus culture (40%).

Methicillin-Resistant Staphylococcus aureus is a Gram-positive bacteria that produces enzyme coagulase, facultatively anaerobic, and can grow optimally at 37°C. Most of the diseases caused by these bacteria produce pus; therefore they are also referred to as pyogenic bacteria.[14,15] Similar results were also shown in a study conducted by Del Mar et al., where pus comprises the majority of the specimens (23%).[16] Forty of all pus specimens in this study came from patients with skin diseases, ulcers, postoperative wounds, malignancies, most of which were skin and soft tissue infections. In addition, there were quite a lot of cases of skin and soft tissue infections that also come from a considerable number of burns patients. This was also confirmed by a study by Bouvet stating that most specimens derived from skin and soft tissue infections (65%).[17]

Two patients with positive MRSA cultures from their CSF specimens was found in this study. A previous study by Leazer stated that the incidence of positive cultures in CSF is very small.[18] The first patient with positive culture in CSF in this study was a one-month-old baby boy diagnosed with hydrocephalus and secondary infection in the postoperative wound with VP shunt installation. MRSA positive culture results were obtained in the pus culture from the surgical wound and CSF culture. *Methicillin-resistant Staphylococcus aureus* meningitis rarely occurs in neonates or children. In one study, the incidence of *S. aureus* meningitis in children was 6%, whereas the incidence for MRSA meningitis was 18%.[19] Central nervous system infection caused by MRSA occurred as a complication of neurosurgical procedures related to the focus of adjacent infection, or hematogenous infection. Hematogenous infection may result from a focal abscess in the postoperative wound or infected ventriculoperitoneal shunt.[18] The second patient was a one-day-old baby girl with a diagnosis of seizure et causa meningitis from the pediatric emergency room. This newborn girl was born prematurely by a traditional birth attendant with a very low weight and did not cry immediately. A positive MRSA culture was obtained from the CSF culture in the second week of treatment. Meningitis due to *S. aureus* and MRSA is commonly seen in very low birth weight and high-risk premature neonates who require prolonged hospitalization with central venous catheter, external devices, and ventilator support.[19]

The specimens in this study came from surgical and non-surgical inpatients with 24 specimens each. The high incidence of MRSA in surgical and non-surgical inpatient wards is suspected to be linked to the fact that most patients were treated for a long period (average 20 days), which could increase the risk of MRSA infection. Based on a study by Sennang et al. in a hospital in Makassar, Indonesia, the length of stay of more than 21.33 days will increase the risk for MRSA infection.[20] This is because MRSA is a pathogen that frequently causes infections in hospitals, resulting in longer hospitalization and higher costs for treatment and infection control requirements.[20] The second-largest number of specimens originated from outpatient care (n=14) with the predominance of outpatient surgery clinics. This shows the importance of improving the hygiene of health workers in this hospital.

Of the total 75 MRSA isolates, 59% were from surgical patients. The high incidence of MRSA in surgical patients is due to many factors. The *Methicillin-resistant* invasive *S. aureus* causes infections in the bloodstream, surgical site (SSI), and pneumonia, which may be life-threatening. The Center for Disease Control and Prevention (CDC) limits SSI to an infection that occurs within 30 days of surgery and after one (1) year of implant surgery. The presence

of *Methicillin-resistant Staphylococcus aureus* in infected wounds leads to higher mortality rate and longer care and hospitalization to increase.[19]

In the year of 2018, the WHO released the global antimicrobial resistance surveillance system (GLASS) report that presents a study in two populations in Thailand: community-acquired bacterial infections (CABI) and hospital-acquired bacterial infections (HABI). In the HABI population group, it was found that 57% were sensitive to Oxacillin and 100% sensitive to vancomycin. Bacteremia due to MRSA was found 0% in the community-acquired S. aureus bacteremia, but 43% in the hospital-acquired S. aureus bacteremia [10]

Data for VRSA in Indonesia is still scarce. A study in Wahidin Sudirohusodo Hospital from January 2015 to December 2016 managed to collect 387 *S. aureus* specimens, with 45 (11%) of them were VRSA. The VRSA specimen was predominantly from male patients (57.8%), with an average age of 41-60 years (35.6%). The treatment room with the most VRSA specimens was the surgical ward (20%). The most common specimens found were blood (28.9%), pus (26.7%), and sputum (20%).[20] Another study in Dr. Hasan Sadikin General Hospital in 2018 observed no VRSA among all *S. aureus* specimens they collected.

In this study, all specimens were sensitive to Linezolid and Tigecycline, and two (3%) inpatient specimens were resistant to vancomycin (VRSA). The first patient was a 29-year-old male with a diagnosis of burns and a sample of a pus culture. The second patient was a 1-day old baby girl with a diagnosis of respiratory distress syndrome and the sample was a blood culture.

When compared to data from GLASS (WHO, 2018), the VRSA rate in Dr. Hasan Sadikin General Hospital was higher (3%) but lower compared to the figures from Wahidin Sudirohusodo hospital.[10] An increasing trend was seen in the VRSA rate in Dr. Hasan Sadikin General Hospital from 0% in 2018 to 3% in 2019 as shown by this study.[6] The increasing number of MRSA and VRSA rates this hospital can be influenced by several risk factors, including length of stay in the hospital, history of surgery, use of invasive medical devices, patients with a history of chronic diseases (such as diabetes, kidney disease), a history of MRSA or previous *Vancomycin-resistant Enterococci* (VRE) infection, and also previous exposure to *Vancomycin* (especially in repeated or prolonged cases). In this study, VRSA results were obtained from pus and blood cultures, which is similar to a study by Saadat et al.[11] which found that VRSA is most commonly found in blood and pus specimens. Vancomycin is a very important antibiotic in patients with MRSA because it is the first line of therapy for MRSA. Given the limited types of antibiotics that are sensitive to MRSA, vancomycin should be placed as a last-line antibiotic or only used for suspected MRSA germs. Good hand hygiene behavior in treatment rooms also provides great leverage for the implementation of clean care standards as a whole, which eventually gives a positive impact on the overall infection control, especially for MRSA and VRSAl.[9]

The limitation of this study is that there is no further explanation regarding the clear source of infection, whether MRSA in the study subjects came from HABI or CABI, and a history of previous antibiotic use.

In conclusion, it is demonstrated in this study that the incidence rate of the MRSA specimens in Dr. Hasan Sadikin General Hospital in 2019 is 17%. The surgical ward is the room where most MRSA specimens are originated. Evaluation and monitoring of antibiotic use showed that all specimens were sensitive to Linezolid and Tigecycline, and two (3%) specimens analyzed during the study period are resistant to Vancomycin.

Based on the result of this study, further research is necessary to understand the incidence of MRSA and to establish measures in the form of routine evaluation and monitoring of antibiotic to control and prevent an increase in the incidence of MRSA, for example by implementing active identification and surveillance of MRSA in surgical patient rooms.

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