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Antibiotics Susceptibility Pattern of MRSA at Intensive Care Room of Ulin General Hospital Banjarmasin

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ABSTRACT

Infection caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA) is a healthcare-associated infection that receives the most significant attention worldwide due to its resistance. Administration of precise and rational antibiotics can prevent high MRSA rates in hospitals. This study aimed to determine the antibiotic susceptibility pattern of MRSA at the intensive care room of Ulin General Hospital, Banjarmasin, between 2016 and 2018. This study was an observational analytic study by taking the results of culture and antibiotic susceptibility pattern data of the MRSA isolated from patients treated at the intensive care room retrospectively. The results showed 37 data of patients suffering from MRSA at the intensive care room in 2016-2018, with a percentage of 23.81%, 25.81%, and 35.19%, respectively. The most common sources of MRSA isolate in this study were sputum (32.39%), blood (29.27%), and pus (16.67%). From 2016 to 2017, there was a decreased susceptibility to macrolide antibiotics, aminoglycosides such as Gentamicin, and quinolones such as Moxifloxacin. In 2018, there was an increased susceptibility pattern of some antibiotics compared to the previous period. Antibiotics with the highest susceptibility in period of 2016-2018 were Linezolid, Quinupristin/Dalfopristin, Tigecycline, Nitrofurantoin, and Trimethoprim/Sulfamethoxazole. Also, the antibiotic with the lowest susceptibility was Tetracycline. It was concluded that there had been changes in some antibiotics' susceptibility pattern to MRSA within 2016-2018.

Keywords: Methicillin-resistant *Staphylococcus aureus*, susceptibility, antibiotics, intensive care room

INTRODUCTION

Treatment of infections caused by *S.aureus* is increasingly difficult since the emergence of Multidrug-Resistant Organism Strains (MDROs) such as Methicillin-Resistant *Staphylococcus aureus* (MRSA). Disease caused by MRSA is one of the most common MDROs associated with healthcare-associated infections and receives the most attention worldwide.[1,2] Reports from Ulin General Hospital, Banjarmasin in 2015 showed that there were 17.64% and 9.09% of positive MRSA cases in January-June and the period of July-December, respectively.[3] The high prevalence of infections caused by the MRSA also resulted in increased annual morbidity and mortality rates of patients.[2,4]

The Centers for Disease Control and Prevention (CDC) reported in 2013 that antibiotic resistance is a global problem, which occurs at an alarming level.[4] The development of bacterial resistance to antibiotics is strongly influenced by antibiotic use intensity in the area because uncontrolled antibiotic use tends to increase bacterial resistance despite initial sensitivity.[5] Studies have found that around 40–62% of antibiotics were used inaccurately for health problems that do not require antibiotics.[1] In addition to the development of new drugs, the use of antibiotics requires monitoring to minimize antibiotic resistance.

The ability of *S.aureus* to quickly respond against every latest antibiotic has become a problem with the development of its resistance mechanisms, starting from Penicillin to the latest with Vancomycin; therefore, it is necessary to identify the antibiotic susceptibility patterns of MRSA in the intensive care room at Ulin General Hospital, Banjarmasin. High resistance rates in the intensive care room can hamper therapy for patients with various infectious diseases since the treatment options are increasingly limited. In addition to the bad immuno-compromised condition of intensive care room patients, the use of some instruments such as

ventilators can increase the risk of entry of pathogens. The situation is incredibly worrying because, generally, patients treated in ICU suffer from severe infections.[5]

This study was expected to help reduce the negative impact that will emerge since it can prolong hospitalization, increase mortality and morbidity, and increase hospitalization costs. Besides, monitoring antibiotic susceptibility patterns must be carried out to identify MRSA bacteria's evolution and the presence of different sensitivity patterns in each region. The results can be used as a primary consideration for the provision of effective empirical therapy, especially in Ulin General Hospital, Banjarmasin.

METHODS

This study was observational analytic research using secondary data of patients with MRSA infection with positive culture test results on all specimens in the Intensive Care Unit (ICU) and Neonatal Intensive Care Unit (NICU) of Ulin General Hospital, from 2016 to 2018. The bacterial antibiotics susceptibility was automatically analyzed using the VITEK® 2 Compact instrument by showing positive cefoxitin screen results for (+) MRSA patients. The results have been validated and interpreted according to the Clinical Laboratory Standard Institute (CLSI).

This study was approved by the Ethics Committee of Ulin General Hospital, Banjarmasin, with ethical clearance number 202/VIII-Reg Riset/RSUDU/19 and by The Committee of Medical Research Ethics of Medical Faculty, Lambung Mangkurat University, with ethical clearance number 445/KEPK-FK UNLAM/EC/IX/2019.

RESULTS AND DISCUSSION

Data were shown in Table 1 according to data from the Clinical Pathology Laboratory of Ulin General Hospital, Banjarmasin.

From 9333 culture requests during 2016-2018, 3763 positive culture tests were obtained in Ulin General Hospital rooms. One thousand one hundred seventy-eight of 3763 results of total positive culture tests were reported from the intensive care room consisting of 741 (62.9%) positive culture results from the ICU and 437 (37.1%) from the NICU. It was identified that among 1178 infectious bacteria in the intensive care room in 2016-2018, 90 (7.64%) of them were *S.aureus,* 37 out of 90 (29.13%) positive *S.aureus* isolates in the intensive care room were MRSA.

The incidence rate of MRSA in the intensive care room of Ulin General Hospital during the period of 2016-2018 continued to increase. This fact might be caused by the lack of attention regarding the prevention of HAIs in hospitals, which facilitates the transmission of cross infections through medical equipment.[6] Also, Kuntaman stated that the irrational use of antibiotics could also trigger antibiotic resistance in a particular area, leading to an increased MRSA incidence.[7] The development of antibiotic resistance is strongly influenced by the intensity of antibiotic exposure in an area.[5,7]

Therefore, it is crucial to evaluate the antibiotic consumption policies through the Antimicrobial Resistance Control Program (ARCP) since 2016 in Ulin General Hospital, which aimed to increase the use of rational drugs to reduce the high number of MRSA. Similar results were obtained from a study conducted by Nuryah *et al.* at Dr. Soeradji Tirtonegoro Hospital. The prevalence of MRSA continued to increase throughout 2015-2018, from 7.69% to 5.63%, 10.85%, and 12.94%.[8]

MRSA infections are closely related to long-term hospitalizations of patients and the possibility of cross-infection through medical equipment, making the ICU an area at high MRSA risk.[9] The distribution sources of *S.aureus* and MRSA isolates in the intensive care room at the Ulin General Hospital can be seen in Table 2.

The results of this study indicated that 30 (25%) positive MRSA infections in ICU and 7 (7.22%) in NICU

Table 1. Frequency and distribution of positive cultures in a period of 2016-2018

Period	Culture Requests	Positive Culture		Positive Culture Intensive Care		Positive *S.aureus*		Positive MRSA	
		(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
2016	2836	1232	43.44	422	34.25	32	7.58	10	23.81
2017	2922	1181	40.42	338	28.62	23	6.81	8	25.81
2018	3575	1350	37.76	418	30.96	35	8.37	19	35.19
Total	9333	3763		1178		90		37	

Table 2. The distribution of hospital unit as sources of *S.aureus* and MRSA isolates in intensive care room at the Ulin General Hospital in a period of 2016-2018

Period	Unit Source	*S.aureus* (n)	MRSA (n)	MRSA (%)
2016	ICU/NICU	26/6	8/2	23.53/25
2017	ICU/NICU	19/4	7/1	26.92/20
2018	ICU/NICU	28/7	15/4	34.88/36.36
Total		90	37	

were found from a total of 90 positive *S.aureus* isolates at Ulin General Hospital in a period of 2016-2018. From 2016 to 2018, 8 (23.53%), 7 (26.92%), and 15 (34.88%) MRSA in the ICU room were found, respectively. In addition, 2 (25%), 1 (20%), and 4 (36.36%) were found in NICU rooms. From a study by Budiman, the prevalence of MRSA colonization in the ICU of Abdul Moeloek Hospital was 37.5%. Intensive care unit-related infections were reported in about 20% of all patients treated in the ICU due to prolonged use of antibiotics and intensive care procedures.[9]

In this study, *S.aureus* and MRSA culture results were obtained from all types of specimens in the form of sputum, blood, pus, fluid, or the patient's wound base. The sample distribution as a source of S.aureus and MRSA isolates in the ICU and NICU of Ulin General Hospital between 2016 and 2018 can be seen in Table 3.

Table 3. The distribution of specimen as sources of S.aureus and MRSA isolates at intensive care room in a period of 2016-2018

Specimen	*S.aureus* (n)	MRSA (n)	MRSA (%)
Sputum	48	23	32.39
Blood	29	12	29.27
Pus	10	2	16.67
Fluid	2	0	0
Wound base	1	0	0
Total	90	37	

Based on the data shown in Table 3, the majority of positive MRSA isolates were obtained from 23 (32.39%) sputum, 12 (29.27%) blood, and 2 (16.67%) pus. These results were following a study conducted by Huang *et al.* from 2014 to 2017 in China; 201 isolates were predominantly obtained from sputum (45.27%), blood (22.88%), urine (8.46%), pus (3.98%), etc.[10] It was also suggested that frequent pneumonia reported in the ICU was associated with the use of ventilators, sepsis, infections of the surgical area, and permanent use of medical devices.[11]

The antibiotic sensitivity pattern of positive MRSA isolates in the intensive care room of Ulin General Hospital in 2016 can be seen in Figure 1.

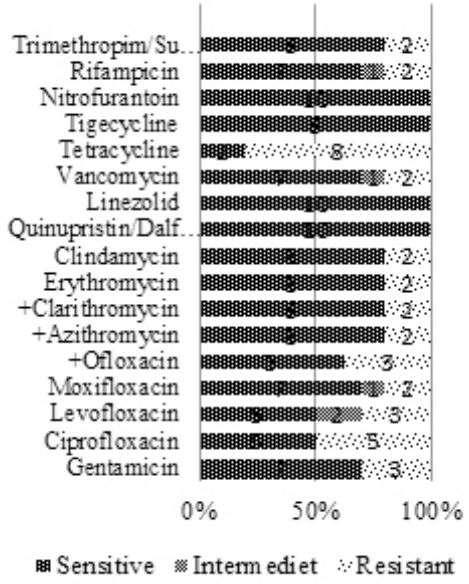

Figure 1. Antibiotic sensitivity pattern of positive MRSA isolates in the intensive care room in 2016

According to the data in 2016, antibiotics with the highest sensitivity (100%) to MRSA isolates were the Quinupristin/Dalfopristin, Linezolid, Tigecycline, and Nitrofurantoin, Followed by Trimethoprim/Sulfamethoxazole, Clindamycin, Erythromycin, Clarithromycin, Azithromycin (sensitivity of 80%), Gentamicin, Moxifloxacin, Vancomycin, and Rifampicin (sensitivity of 70%), Ofloxacin (sensitivity of 62.5%), Ciprofloxacin (sensitivity of 50%) and Levofloxacin (sensitivity of 50%), while the antibiotic with the lowest antibiotic sensitivity (20%) was Tetracycline. It was also found that the antibiotics with intermediate sensitivity were Levofloxacin (sensitivity of 20%), Moxifloxacin (sensitivity of 10%), Vancomycin (sensitivity of 10%), and Rifampicin (sensitivity of 10%). In addition, without proper monitoring, the use of these antibiotics can lead to antibiotic resistance.

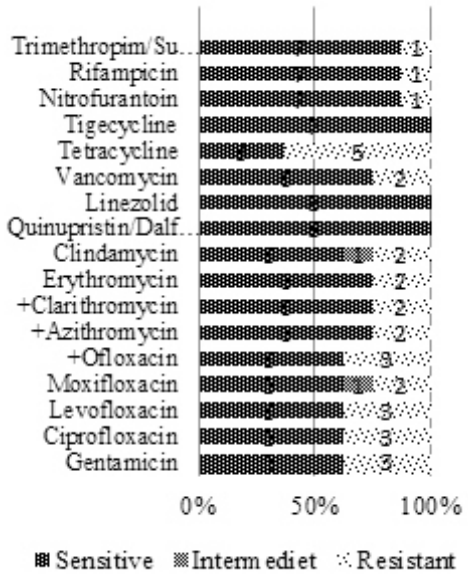

Figure 2. Antibiotic sensitivity pattern of positive MRSA isolates in the intensive care room in 2017

According to the data in 2017, the antibiotics with the highest sensitivity (100%) against MRSA isolates were Quinupristin/Dalfopristin, Linezolid, and Tigecycline. There was a decrease in Nitrofurantoin sensitivity, a common drug of choice for urinary tract infections (87.5%). It was followed by Rifampicin and Trimethoprim/Sulfamethoxazole (87.5%), Erythromycin, Clarithromycin, Azithromycin, and Vancomycin (75%), Gentamicin, Moxifloxacin, Ofloxacin, Ciprofloxacin, Levofloxacin, and Clindamycin (62.5%). Tetracycline remained an antibiotic with the lowest sensitivity (37.5%), while intermediate sensitivity (12.5%) was found in both Moxifloxacin and Clindamycin. The sensitivity of Moxifloxacin decreased from (70%) to (62.5%). The sensitivity of Clindamycin decreased from (80%) to (62.5%). This fact indicated that there had been no improvement in the use of antibiotics Moxifloxacin and Clindamycin compared to the previous year.

In 2018, Quinupristin/Dalfopristin, Linezolid, Tigecycline, and Nitrofurantoin remained the antibiotics with the best sensitivity (100%) to MRSA isolates, followed by Rifampicin, Vancomycin, Trimethoprim/Sulfamethoxazole, Erythromycin, Clarithromycin, Azithromycin, and Gentamicin (89.5%), Moxifloxacin and Levofloxacin (84.2%), Ofloxacin (83.3%), Ciprofloxacin (78.5%), Clindamycin (73.7%). However, Tetracycline still had the lowest sensitivity (47.4%). This study showed that antibiotics with decreased sensitivity this year were Moxifloxacin, Ciprofloxacin, and Clindamycin (5.3%) and Vancomycin (5.25%). It was shown that all antibiotics used in this study increased sensitivity to MRSA isolates, although the incidence of MRSA cases significantly increased compared to the previous year.

The highest antibiotic sensitivity during 2016-2018 was Linezolid, Tigecycline, Quinupristin/Dalfopristin, and Nitrofurantoin. This finding might be due to the highly supervised prescription in administering these antibiotics. Thus their use can be controlled and according to appropriate therapeutic indications, especially for infections with intolerable resistance to other antibiotics. There has been a decrease in antibiotic sensitivity in 2017 from the previous year. In 2018, the sensitivity of antibiotics to MRSA isolates increased from 2017. This result might be due to antibiotic restrictions in hospitals and the ARCP program running well from the previous year, which on average decreased sensitivity from 2016. Although it showed an increase in sensitivity, Tetracycline is still not recommended as a therapy for MRSA patients because the sensitivity is still below 60%.

Similar results were obtained from research by Kurniawan *et al.* at Dr. Soeradji Tirtonegoro Hospital, that 64.8% of *S.aureus* isolates were resistant to Tetracycline, indicating that sensitivity to antibiotics was only 35.2%. Also, it was also found that 53.7% were resistant to Erythromycin, and 40.7% were resistant to Cloxacillin.[8] In a study conducted by Hilda and Berlina in 2015 at Health Laboratory, East Kalimantan, 79.5% isolates were reported to be resistant against Penicillin, 34.6% were resistant to

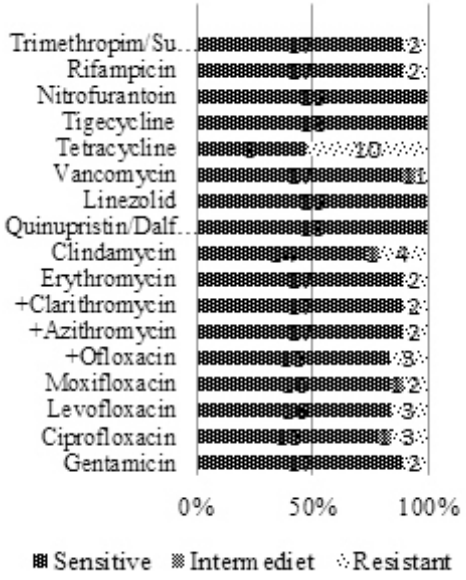

Figure 3. Antibiotic sensitivity pattern of positive MRSA isolates in the intensive care room in 2018

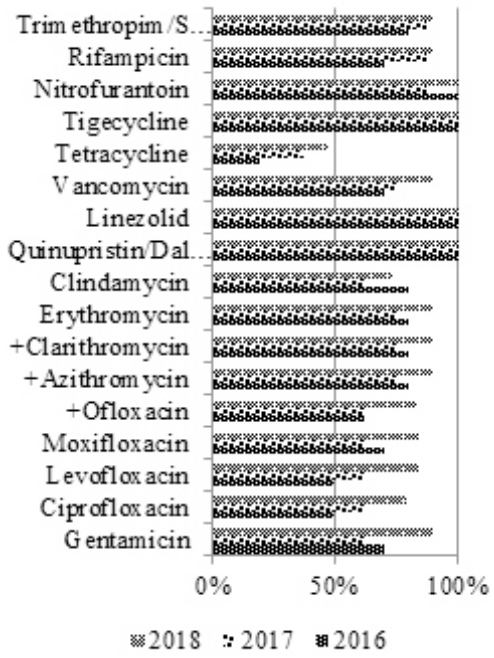

Figure 4. The development of antibiotic sensitivity against MRSA in the intensive care room at Ulin General Hospital in the period of 2016-2018

Gentamicin, and 33.3% were resistant to Ciprofloxacin.[8]

This result was also consistent with a study by Nasution, which stated that in addition to its resistance to all β-lactam antibiotics, MRSA was also less sensitive to antibiotics from Lincosamide, Macrolide, Aminoglycoside, and Fluoroquinolone groups.[12] In research at Ulin General Hospital, the Lincosamide sensitivity, Clindamycin, decreased from 80% in 2016 to 62.5% in 2017 and 73.7% in 2018. This result could be due to the exclusive administration of Clindamycin because of its superior activity against organisms in its spectrum such as *Staphylococcus*, *Streptococcus*, and some anaerobic bacterias.[13] However, due to several factors such as inappropriate use, large amounts of prescription, and a combination of more intensive use of antibiotics with very sensitive patients against infection caused a decreased sensitivity of antibiotics.[14] The HA-MRSA isolate has shown to be resistant against Clindamycin, especially in children.[15]

The sensitivity of Gentamicin, a member of the aminoglycoside group, decreased from 70% in 2016 to 62.5% in 2017. The research results by Refdanita *et al.* showed that the activity of Aminoglycoside antibiotics against *S.aureus* had a resistance of 33.3%.[14] The more significant number of Gentamicin resistance of 41.67% was shown in a study by Sulistyaningrum *et al.*[16] In a study by Erika at Dr. Saiful Anwar Hospital, Malang from 2010 to 2014, MRSA isolates from blood and pus specimens had a resistance rate of >50% against Gentamicin.[17]

The sensitivity of one of Fluoroquinolone, Ciprofloxacin, increased from 50%, 62.5%, to 78.9% in the three-year periods. The results were similar to Erika's research from 2010 to 2014, which showed a resistance rate (> 50%) of MRSA isolates from blood and pus specimens against Ciprofloxacin.[17] In the study by Sulistyaningrum *et al.*, the Ciprofloxacin antibiotic resistance test results were 41.67%.[16]

Tetracycline has the lowest sensitivity of 20%, 37.5%, and 47.4% in the three periods, indicating that its use was no longer sufficient. A study by Vinandryano at Dr. Soetomo Hospital, Surabaya, also found that about 70% of *S.aureus* were resistant to Tetracycline.[18] Tetracycline's mechanism of action is different from the β-lactam antibiotics because it will inhibit protein synthesis by bonding a small 30S ribosomal subunit with aminoacyl tRNA on the side (A-amino acid) of a large 50S unit located in the ribosome-mRNA complex. Movement of tRNA inhibition to bind causes disruption of the formation of polypeptide chains. This resistance mechanism is due to a shift in the introduction of the Tetracycline target, causing less affinity or changes in antibiotic uptake due to reduced permeability of the pathogenic membrane known as the efflux mechanism. This efflux process is a process in which a membrane protein as a single transporter can move some antibiotics from within the cell to the substrate to make the bacteria resistant to Tetracycline.

S.aureus was also resistant to the glycopeptide group, such as Vancomycin, a drug of choice in MRSA therapy. It can be caused by the irrational use of Vancomycin over a long period.[19] In 3 consecutive years, especially in the intensive care room of Ulin General Hospital, the sensitivity of Vancomycin has improved, from 70% to 75% and 89.5% in 2018. However, in the study of Dwiyanti *et al.* at the Ratu Zalecha Regional Hospital, Martapura, there were 7 (26%) MRSA and VRSA samples from 14 *S.aureus* paramedic nasal swab samples in the surgical wards and ICU, and 6 (22%) samples were a combination of MRSA and VRSA.[19]

The emergence of resistant strains can cause differences in antibiotic sensitivity patterns in various studies performed at different times due to irrational use of antibiotics. The use of antibiotics as a prophylactic treatment in hospital care can also be related to the high percentage of resistance. Current guidelines recommend narrow-spectrum antibiotics as antimicrobial prophylaxis in surgery, such as

Cefazolin, for most surgical procedures or Cefoxitin for abdominal surgery.[20]

However, since this study was not based on the patient's clinical condition or as the history of previous antibiotic use, some factors of change in sensitivity of the antibiotic were unable to be evaluated. Therefore, further study was needed to analyze the factors that can influence antibiotic sensitivity patterns in the intensive care room at Ulin General Hospital.

CONCLUSION AND SUGGESTION

Antibiotics with the highest sensitivity to positive MRSA isolates in the intensive care room of Ulin General Hospital, Banjarmasin in period of 2016-2018 were Quinupristin/Dalfopristin, Linezolid, Tigecycline and Nitrofurantoin, followed by Trimethoprim/Sulfamethoxazole, Rifampicin, Azithromycin, Clarithromycin, Erythromycin, Vancomycin, Clindamycin, Gentamycin, Moxifloxacin, Ofloxacin, Levofloxacin, and Ciprofloxacin. Also, the antibiotic with the lowest sensitivity was Tetracycline. It was shown that all members of the beta-lactam antibiotic group and their derivatives were resistant throughout 2016-2018.

Studies regarding the antibiotic sensitivity pattern to MRSA in the intensive care room must be periodically conducted to determine the trend of antibiotic sensitivity changes to positive MRSA isolates each period. The data obtained can be used as a guide in the selection of appropriate empirical therapy. Further research was required to analyze the factors that can influence antibiotic resistance to MRSA in Ulin General Hospital by considering patients' clinical condition, prior antibiotic use, or running status of the program set by ARCP.

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