

Vancomycin Monotherapy vs Alternative Antibiotics for MRSA Patients: A Systematic Review

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ABSTRACT

Background: MRSA (Methicillin-resistant *Staphylococcus Aureus*) has become a global epidemic at a high rate. MRSA is one of the most difficult infections to treat because of its resistance to several antibiotics. Nowadays, there are still many antibiotics for MRSA in the world. This study discusses antibiotic usage against MRSA infection. It expects to contribute to the third SDG in terms of infection therapy.

Method: Seven studies used for this systematic review study were conducted through PubMed and ClinicalTrials.gov databases.

Aims: This study compared MRSA patients treated with vancomycin monotherapy and alternative antibiotics.

Result: The highest use alternative antibiotics besides vancomycin were linezolid with 27.8%, cotrimoxazole 8.1%, daptomycin was 6.7%, and combination vancomycin plus flucloxacillin was 3.2%. Treatment duration for MRSA, treated using vancomycin compared with alternative antibiotics, did not show a significant difference. Patients treated using vancomycin mostly had higher mortality than the alternative antibiotics. The most dominant age infected by MRSA is the elderly population. Gender dominated by males 59.4% (range from 32.5% to 71.4%). The main comorbidity of the patients was heart disease, diabetes mellitus, and lung disease.

Conclusion: Alternative antibiotics mostly have lower mortality compared to vancomycin. Insignificant treatment duration appears between vancomycin and alternative antibiotics. Most patients with MRSA were elderly, male, and patients with comorbid heart disease, diabetes mellitus, and lung disease.

Keywords: MRSA; methicillin-resistant *staphylococcus aureus*; infection; vancomycin; alternative antibiotic

INTRODUCTION

MRSA or Methicillin-resistant *Staphylococcus aureus* is one type of bacteria that is difficult to treat because it is resistant to beta-lactam antibiotics, including methicillin, oxacillin, penicillin, and amoxicillin. MRSA resistance occurs because of the *mecA* gene that produces a penicillin-binding protein (PBP2a) with a low affinity for beta-lactam antibiotics [1]. Based on data from WHO, MRSA has become an epidemic that spreads globally in several countries, including the United States, Canada, Japan, and Indonesia [2]. It is often associated with overuse and misuse of antibiotics.

Several recent studies, especially those focused on antibiotics against MRSA, have been carried out in various countries. One of them is an experimental study conducted at a local hospital in Jordan that found vancomycin is the most effective antimicrobial and is the drug of choice against MRSA [3]. Another study also conducted in Trivandrum, India, in 2018 showed that all MRSA isolates were sensitive to the linezolid and vancomycin [4]. In Indonesia, an analytical study conducted in 2019 showed that the antibiotic chloramphenicol is very sensitive for MRSA, although it is not under therapeutic guidelines for MRSA [5].

However, vancomycin remains the gold standard treatment option for MRSA. Most physicians use vancomycin for empirical and definitive therapy to treat MRSA as outlined in the Infectious Disease Society of America (IDSA) guidelines [6]. However, alternative antibiotics are needed to treat MRSA due to the limited distribution of vancomycin into tissues and the emergence of MRSA bacterial isolates that are resistant to vancomycin.

Based on the variation of antibiotic therapy against MRSA in various places and the above facts, there are several opportunities for developing research on vancomycin monotherapy versus alternative antibiotics as a therapy

for MRSA. In addition, this study is critical because the incidence of MRSA is still high due to several factors, as previously described. Therefore, we conducted a systematic review to compare vancomycin monotherapy and alternative antibiotics to treat MRSA patients. This study also considers characteristics by identifying age, gender, and comorbidities.

METHOD

2.1 Study design

This research is secondary in a systematic review that follows the PRISMA guidelines.

2.2 Search strategy

We conducted a systematic review to identify studies comparing vancomycin monotherapy with alternative antibiotics to determine the most effective antibiotic for treating MRSA patients. A literature search in this study was conducted through the PubMed and ClinicalTrial.gov electronic databases to identify relevant studies systematically. A literature search was using boolean operators including OR/AND with search terms including (MRSA) AND (methicillin-resistant staphylococcus aureus)) AND (methicillin-resistant)) AND (vancomycin)) OR (clindamycin)) OR (linezolid)) OR (trimethoprim)) OR (sulfamethoxazole)) OR (tigecycline)) OR (telavancin)) OR (ceftaroline)) OR (daptomycin)) OR (oxazolidinones)) OR (beta-lactam)) AND (outcome)) AND (treatment outcome)) AND (mortality). The keywords used were entered into an electronic database search engine using an advanced search.

2.3 Inclusion and exclusion criteria

Included studies met the following inclusion criteria:

- Literature published in 2010-2020
- Literature published in English or Indonesian
- The literature includes patients aged over 18 years who have a positive culture of MRSA

The exclusion criteria of this study are:

- Full-text of literature not available
- The literature includes patients with positive culture results for MRSA and having a bacterial infection other than MRSA

2.4 Data extraction

The investigator independently screened and assessed the title and abstracts before full-text retrieval. The data extracted from these studies included the author, year of publication, research method, number of research participants, given intervention, inclusion criteria, exclusion criteria, and variables. Excel 2010 (Microsoft Corporation) software program used to organize extracted study data.

2.5 Quality assessment

The two reviewers independently assessed the quality of the study using the Mixed Method Appraisal Tools (MMAT). This tool consists of 5 study categories, consisting of 5 questions each. There are three kinds of answers given to answer the points above, namely yes (Y), no (N), cannot tell (C). The final result has obtained all answers whether the journal can be included (include) or not (exclude).

2.6 Data synthesis

The results of the distribution of data classified based on research variables are present in the frequency distribution table in a descriptive format. Variables extracted from each publication distinguished between vancomycin monotherapy and alternative antibiotics. A meta-analysis was not performed because there was wide variability in the study designs used.

RESULTS

3.1 Study selection

All 718 studies were found on keyword searches through 2 databases, PubMed and ClinicalTrials.gov, as shown in Figure 1. Then out of 718 studies, two duplicate articles were removed, leaving 716 articles. Researchers screened based on titles and abstracts that matched the topic and excluded 679 less relevant studies. From 37 articles reviewed by accessing the full-text literature, 16 studies did not compare vancomycin with other antibiotic therapy. Six studies were not suitable for control antibiotics, 1 study used animal samples, 1 study sample included non-MRSA patients, three studies did not contain all the variables needed, and three studies included <18 years patients. Seven articles met the inclusion and exclusion criteria included in this systematic review. The included studies are present in Table 1.

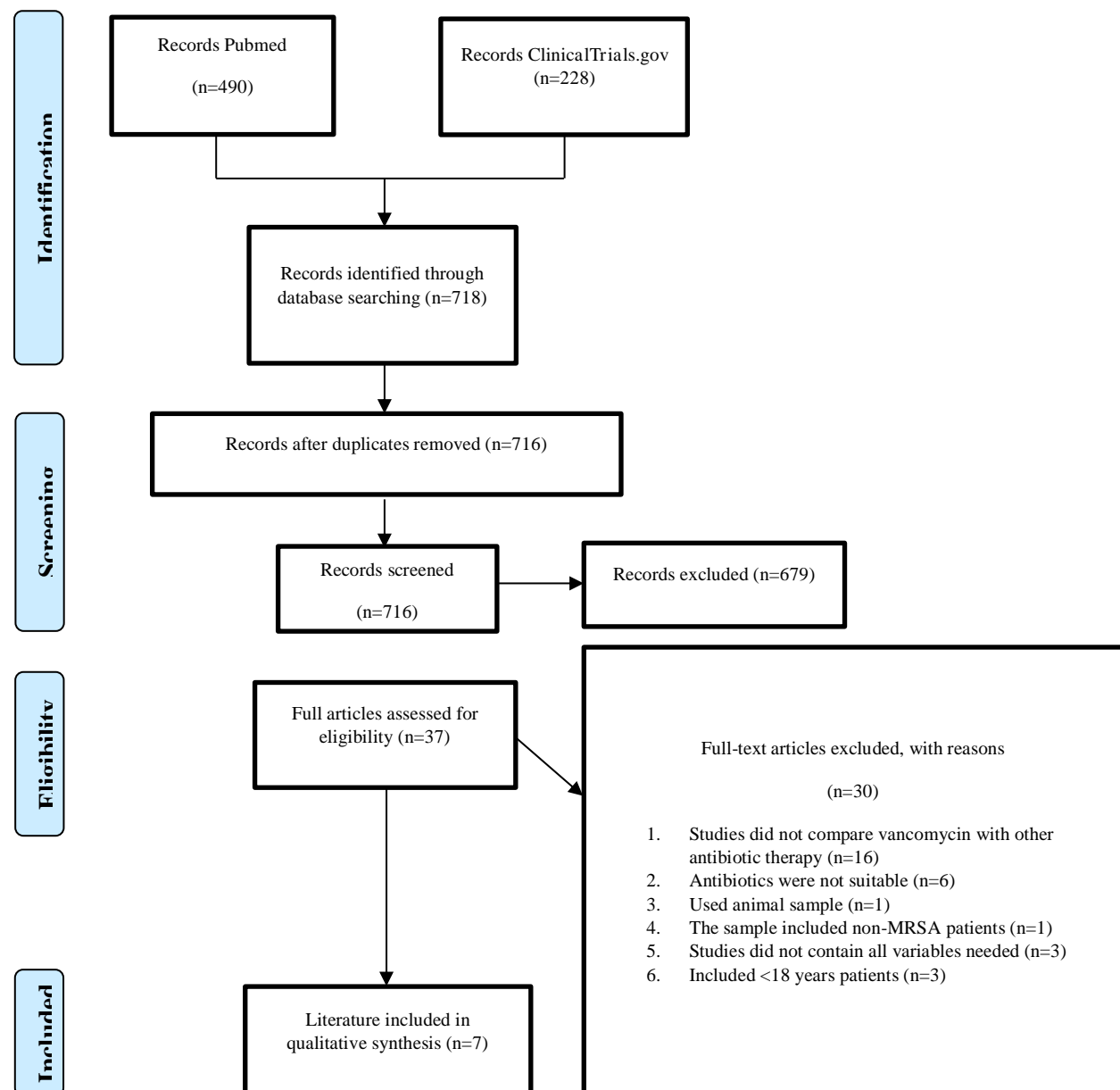


Figure 1. Study selection flow chart for systematic review

Table 1. Included Studies in Our Systematic Reviews

Author (Year)	Country	Researches Methods	Sample	Number of MRSA patients (n)
Goldberg et al. (2010)	Israel	Retrospective cohort study	MRSA bacteremia patients from 1998 to 2007	114
Moore et al. (2011)	United States	Retrospective case-control study	MRSA bloodstream infection (BSI) patients from 2005 to 2009 in Detroit Hospital, Michigan	177
Wunderink et al. (2012)	Paris	Randomized control study	Positive culture MRSA patients from 13 th October 2004 to 31 st January 2010	348
Peyrani et al. (2014)	United States	Retrospective observational study	MRSA VAP patients in ICU treated with linezolid or vancomycin from November 2008 to October 2012	188
Davis et al. (2015)	Australia	Multicenter randomized control trial	Positive culture MRSA patients in 7 Australian Hospital from January 2011 to May 2014	60
Eliakem-Raz et al. (2016)	Israel	Retrospective case-control study	MRSA pneumonia patients in Beilinson Hospital, Israel, from January 2010 to December 2015	81
Kalimuddin et al. (2018)	Singapore	Randomized controlled phase 2B trial	MRSA bloodstream infection (BSI) patients in third Hospital Singapura from 13 th February 2014 to 25 th September 2015	14
Total Sample				982

Antibiotic Therapy for MRSA Patients

Table 2. The table below shows control antibiotic and alternative antibiotic treatment for MRSA patients

Literature (Year)	Control Antibiotic		Alternative Antibiotic			Total
	Vancomycin (%)	Cotrimoxazole (%)	Daptomycin (%)	Linezolid (%)	Vancomycin + Flucloxacillin (%)	
Goldberg et al. (2010)	76	38	0	0	0	114
Moore et al. (2012)	118	0	59	0	0	177
Wunderink et al. (2012)	176	0	0	172	0	348
Peyrani et al. (2014)	87	0	0	101	0	188
Davis et al. (2016)	29	0	0	0	31	60
Eliakem-Raz et al. (2016)	39	42	0	0	0	81
Kalimuddin et al. (2018)	7	0	7	0	0	14
Total	532 (54,2%)	80 (8,1%)	66 (6,7%)	273 (27,8%)	31 (3,2%)	982

Dosage, Interval, and Administration Route of Antibiotics

Table 3. The table below shows the dosage, interval, and administration route of antibiotic treatment for MRSA patients

Literature (Year)	Sample	Antibiotic Therapy	
		Control Antibiotic	Alternative Antibiotic
Goldberg et al. (2010)	MRSA bacteremia	Vancomycin IV	Cotrimoxazole IV or oral
Moore et al. (2011)	MRSA bloodstream infection (BSI)	Vancomycin IV 10-20 µg/mL	Daptomycin 6 mg/kg every 24 h
Wunderink et al. (2012)	MRSA pneumonia	Vancomycin IV 15mg/kg every 12 h	Linezolid IV 600 mg every 12 h
Peyrani et al. (2014)	MRSA pneumonia	Not listed	Not listed
Davis et al. (2015)	MRSA bacteremia	Vancomycin IV 1.5 g twice daily	Flucloxacillin IV 2 g every 6 h
Eliakem-Raz et al. (2016)	MRSA pneumonia	Vancomycin 1 g twice daily	Trimethoprim IV 160 mg combined with sulfamethoxazole IV 800 mg twice daily
Kalimuddin et al. (2018)	MRSA bloodstream infection (BSI)	Vancomycin IV 15 mg/kg every 12 h	Daptomycin IV 6mg/kg every 24 h

h: hour; IV: Intravena

Duration of Treatment Vancomycin Monotherapy and Alternative Antibiotics in MRSA Patients

Table 4. The table below shows the duration of treatment MRSA patients treated with vancomycin and alternative antibiotics

Literature (Year)	Median Length of Treatment (days)				
	Vancomycin (Control)	Cotrimoxazole	Daptomycin	Linezolid	Vancomycin + Flucloxacillin
Goldberg et al. (2010)	25 (2 - 244)	21,5 (3 - 158)			
Moore et al. (2012)	12 (8 -18)		15 (10 - 24)		
Wunderink et al. (2012)	10 (2 - 22)			10 (2 - 22)	
Peyrani et al. (2014)	16			18	
Davis et al. (2016)	1 (1 -2)				1 (1 - 4)
Eliakem-Raz et al.	33 (3 - 97)	23,5 (3 - 74)			

(2016)

Kalimuddin et al. (2018)

15 (14 - 41)

15 (14 - 27)

Mortality Outcome Vancomycin Monotherapy and Alternative Antibiotics in MRSA Patients

Table 5. The table below shows the mortality outcome of MRSA patients treated with vancomycin and alternative antibiotic

Literature (Year)	Mortality Outcome = n (%)				
	14-day mortality	28-day mortality	30-day mortality	60-day mortality	90-day mortality
Goldberg et al. (2010)					
Vancomycin (Control), N = 76			31 (40,8%)		
Cotrimoxazole N = 38			13 (34,2%)		
Moore et al. (2012)					
Vancomycin (Control), N = 118				24 (20,3%)	
Daptomycin N = 59				5 (8,5%)	
Wunderink et al. (2012)					
Vancomycin (Control), N = 176				30 (17%)	
Linezolid N = 172				27 (15,7%)	
Peyrani et al. (2014)					
Vancomycin (Control), N = 87	8 (9,2%)				
Linezolid N = 101	10 (9,9%)				
Davis et al. (2016)					
Vancomycin (Control), N = 29		5 (17,2%)			6 (20,7%)
Vancomycin + Flucloxacillin N = 31		5 (16,1%)			5 (16,1%)
Eliakem-Raz et al. (2016)					
Vancomycin (Control), N = 39			20 (51,3%)		
Cotrimoxazole N = 42			11 (26,2%)		
Kalimuddin et al. (2018)					

Vancomycin (Control), N = 7

1 (14,3%)

Daptomycin N = 7

0 (0%)

MRSA Patients' Characteristic

Table 6. The table below shows patients' characteristics consisting of age, gender, and comorbidities

Author (Year)	Goldberg et al. (2010)	Moore et al. (2012)	Wunderink et al. (2012)	Peyrani et al. (2014)	Davis et al. (2016)	Eliakem-Raz et al. (2016)	Kalimuddin et al (2018)	Total
Age								
Mean age (years)	75.3	51.5	61.2	57.5	64.5	72,5	67,5	
Interpretation	Old age	Middle age	Elderly	Middle age	Elderly	Elderly	Elderly	
Gender								
Male	37 (32.5%)	110 (62.1%)	228 (65.5%)	112 (59.6%)	39 (65%)	47 (58%)	10 (71.4%)	583 (59.4%)
Female	77 (67.5%)	67 (37.9%)	120 (34.5%)	76 (40.4%)	21 (35%)	34 (42%)	4 (28.6%)	399 (40.6%)
Total	114	177	348	188	60	81	14	982
Comorbidity								
Diabetes mellitus	49	68	136	46	24		2	325
Heart disease	72	69	203	54				398
Neurological disorder		18						18
Malignancy		21		13				34
Renal disorder		106	113	14	12		5	250
Vascular disease	31	16		47				94
Lung disease		15	235	23	16	18		307
HIV/AIDS		13						13
Immunocompromised		31						31
Peptic ulcer disease		5						5
Liver disease				10	5			15
Respiratory disease				42				42
Decubitus Ulcer	18							18

DISCUSSION

4.1 Antibiotic Therapy for MRSA Patients

Among 982 patients, it found that the most alternative antibiotics used to treat MRSA patients were linezolid as many as 273 patients or 27.8%, followed by cotrimoxazole as many as 80 patients or 8.1%, daptomycin as many as 66 patients or 6.7%, and the combination of vancomycin plus flucloxacillin in 31 patients or 3.2%.

Several previous studies have shown that vancomycin is the primary therapy for MRSA [7]. The reason is that vancomycin is the drug of choice for most MRSA patients [8]. However, the widespread and excessive use of vancomycin can lead to its resistance. Researchers recently said that the distribution of vancomycin into tissues was

limited, and the emergence of MRSA bacterial isolates that were resistant to vancomycin required alternative antibiotics to treat MRSA [9].

The most commonly used alternative antibiotic was linezolid (27.8%). This result supports by a previous study that linezolid is the most commonly used antibiotic to treat MRSA patients with as many as 51.60% [10]. Linezolid demonstrated superior properties of vancomycin to treat MRSA, especially in cases where there was a high MIC (2 mg/L) for vancomycin [11]. In addition, linezolid is more likely to respond better than patients treated with vancomycin [12].

Cotrimoxazole used for alternative therapy for MRSA patients was 8.1%. In another study, cotrimoxazole has also been used as an alternative to vancomycin. It stated that trimethoprim-sulfamethoxazole is superior to vancomycin for the treatment of MRSA patients and may be an adjunct therapy option for MRSA patients [13].

Daptomycin used for alternative therapy in MRSA patients was 6.7%. Another study also reviewed the use of daptomycin for MRSA patients. It declares that daptomycin is superior to vancomycin in MRSA with high MIC [13]. These findings support recent guideline recommendations, which suggest switching to alternative agents such as daptomycin when isolates have high vancomycin MICs or when patients do not improve during treatment.

The combination of vancomycin plus flucloxacillin used as an alternative therapy for MRSA patients was 3.2%. Compared with other alternative antibiotics, this antibiotic combination for MRSA patients is not too much. This study found that the combination of antistaphylococcal beta-lactam antibiotics with vancomycin can shorten the duration of MRSA bacteraemia [14].

4.2 Duration of Treatment Vancomycin Monotherapy and Alternative Antibiotics in MRSA Patients

The results showed that the median duration of treatment for MRSA patients between patients receiving control antibiotic therapy (vancomycin) and alternative antibiotics, namely cotrimoxazole, daptomycin, linezolid, and the combination of vancomycin plus flucloxacillin did not show a significant difference.

The two studies comparing vancomycin and cotrimoxazole stated that the treatment duration for patients treated by the two antibiotics did not have a significant difference [13,15]. However, the duration of treatment in patients treated with the antibiotic cotrimoxazole is shorter than the antibiotic vancomycin, possibly due to the superiority of cotrimoxazole over vancomycin against intracellular phagocytes of MRSA, thereby achieving a higher clearance rate than vancomycin [15].

A study comparing vancomycin and daptomycin stated that the treatment duration for patients treated by the two antibiotics did not have a significant difference. There is no difference between the vancomycin and daptomycin antibiotics for the patients' length of stay. Based on these studies, it stated that daptomycin has a greater success rate than standard therapy. However, almost all RSA isolates in this study had MIC < 1 g/ml, so it is difficult to conclude whether daptomycin is superior to vancomycin in treating MRSA patients with higher vancomycin MIC [16].

The two studies comparing vancomycin and linezolid stated that the duration of treatment for patients treated by the two antibiotics did not have a significant difference [17,18]. It showed that patients who had received linezolid therapy more than three times were likely to be discharged with oral MRSA antibiotics indicating that patients in the linezolid group were discharged early to complete continued home therapy with oral medications. In contrast, the patients of vancomycin had to remain in the hospital until therapy was complete. However, if the linezolid is given intravenously, it does not reduce the length of hospital stay compared to vancomycin [19].

A study comparing vancomycin monotherapy and a combination of vancomycin plus flucloxacillin stated that the duration of treatment for patients treated by the two antibiotics was the same, and no significant difference was found [20].

4.3 Mortality Outcome Vancomycin Monotherapy and Alternative Antibiotics in MRSA Patients

From the seven previously selected literature, almost all of the literature showed that MRSA patients given vancomycin had higher mortality than alternative antibiotics, namely cotrimoxazole, daptomycin, linezolid, and the combination of vancomycin plus flucloxacillin.

Two studies that compare vancomycin and cotrimoxazole found that the mortality rate of patients in the vancomycin group was significantly greater than that in the cotrimoxazole group 40.8% and 51.3%, respectively [13,15]. Cotrimoxazole has low toxicity and is still acceptable to the body. Compared to vancomycin, cotrimoxazole has a higher clearance rate and exhibits rapid bactericidal activity [15]. Treatment failure in the vancomycin group may also be due to poor penetration of vancomycin into lung tissue and lung epithelial lining fluid in MRSA patients [13].

Two other studies comparing vancomycin and daptomycin found that the mortality of patients treated with vancomycin was significantly higher than daptomycin as many as 20.3% and 14.3%, respectively [16,21]. The study suggested that MRSA with a high vancomycin MIC may be associated with poorer clinical outcomes in patients on the vancomycin group compared with alternative MRSA antibiotics such as daptomycin [16]. In addition, the bactericidal activity of daptomycin is rapid, thereby contributing to improved patient clinical outcomes [22].

A study comparing vancomycin and linezolid showed that the mortality rate in the group of patients given vancomycin was higher than linezolid as many as 17% [17]. However, there are slightly different results of the other study. This study showed that the mortality of patients with vancomycin was lower than those of alternative antibiotics, namely 9.2% [12]. It may be due since this study only conducted up to 14-day mortality rates and had not been studied further.

Based on a study that compared vancomycin monotherapy and a combination of vancomycin plus flucloxacillin, the results showed that the group of patients given vancomycin had a higher mortality rate than the combination of vancomycin and flucloxacillin antibiotics, which was 20.7%. It could be due to vancomycin monotherapy showing slower bactericidal activity, poorer tissue penetration, and slower clearance of bacteremia. In addition, the combination of vancomycin and beta-lactam antibiotics was able to induce potentiation of host defense against *Staphylococcus aureus* bacteria which would reduce transcription of the *mecA* gene [14].

4.4 MRSA Patients' Characteristic

The most dominant mean age group in MRSA patients was elderly patients. A previous study in Spain supports the result of this study that the most dominant age group was the elderly (39.9%) [23]. Based on this, the elderly population is highly susceptible to MRSA due to their chronic illness, exposure to multiple antibiotics in the past that made resistance to some drugs, the use of invasive devices that debilitate, reduce mobility, and impair the immune response [24].

This study showed that male MRSA patients were 583 or 9.4% (range 32.5% - 71.4%). The previous research supports the result of this study that there were more male MRSA patients (69.6%) [5]. It can be affected by several factors, such as poor hand hygiene rates in the male population compared to the female population, and it is also influenced by the hormone possessed by the female population, namely estrogen, which may affect the virulence factor *Staphylococcus aureus* bacteria [25].

The results of this study showed that MRSA patients had the most dominant comorbidities with heart disease (398), diabetes mellitus (325), and lung disease (307), respectively. The most dominant comorbidities of MRSA patients in this study differed from previous studies, which showed that diabetes mellitus was the main comorbid MRSA [26]. Several factors influence this, including that patients with diabetes mellitus are a significant risk factor for MRSA infection in pedis ulcers. It will increase the risk of colonization due to damage to the skin barrier and act as a gateway for infection. Patients with diabetes will experience a decreased immune response characterized by impaired granulocyte attachment, chemotaxis, and phagocytosis, making the patient susceptible to infection [27]. The difference in this study's data can also be caused by the large variety of diseases classified as heart disease. The third most common comorbidity, namely lung disease, was probably caused by 3 of the seven pieces of literature used in this study used samples of MRSA pneumonia patients.

CONCLUSION

The most common alternative antibiotic for MRSA patients is linezolid. The duration of treatment for MRSA between patients receiving vancomycin and alternative antibiotics did not show a significant difference. Almost all of the literature showed that the group of MRSA patients given vancomycin had higher mortality than

alternative antibiotics. Most of the patients were elderly, male, and had heart disease, diabetes mellitus, and lung disease comorbidities. Consideration should be given to the guideline recommendations suggesting switching to alternative antibiotics when the MRSA bacterial isolate has a high vancomycin MIC or if the patient does not improve during therapy. Research analytical methods to identify and analyze the most suitable alternative antibiotics for patients with MRSA bacterial infection may be needed.

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CONFLICT OF INTEREST

Neither of the authors has any conflict of interest that may interfere with the result of this study.

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