ISSN 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

Effectiveness evaluation of antibiotic use in patients with *Methicillin-resistant Staphylococcus aureus* (MRSA) infection: a review

Musdalifa As[1*], Ika Puspitasari[1,2], Titik Nuryastuti[3]

[1]Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, [2]Gadjah Mada Academic Hospital, Yogyakarta, [3]Department of Microbiology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta

https://doi.org/

Submitted: 17-11-2023
Accepted : 02-01-2024

Keywords:
antibiotic;
Methicillin-resistant Staphylococcus aureus (MRSA);
rational use;
infection;
resistance

ABSTRACT

Methicillin-resistant Staphylococcus aureus (MRSA) is a pathogen that become a public health problem due to its ability to be resistant to more than three classes of antibiotics. Evaluation of the effectiveness of antibiotic use in patients with MRSA is important to optimize antibiotic use and to control antibiotic resistance. This article review attempted to evaluate the effectiveness of antibiotics in patients with MRSA. This review explored the results of previous research from PubMed as a literature source and the PRISMA flow diagram as a protocol for the article selection process. Eight studies reviewed the evaluation of the effectiveness of antibiotic use in MRSA patients with various clinical conditions, such as uncomplicated wound infections, cellulitis and no wound, purulent drainage or abscess, cSSSI infections caused by MRSA, infections caused by MRSA bacteremia and nosocomial infections caused by MRSA. In conclusion, the effectiveness of antibiotics in patients with MRSA infection depends on the clinical condition of each patient. Therefore, the use of antibiotics is adjusted based on the type of infection and the efficacy of the antibiotics. Combination therapy is recommended for MRSA patients considering its life-threatening ability.

ABSTRAK

Methicillin-resistant Staphylococcus aureus (MRSA) merupakan patogen yang menjadi maslah kesehatan masyarakat karena kemampuannya menimbulkan resistensi terhadap lebih dari tiga golongan antibiotik. Evaluasi efektivitas penggunaan antibiotik pasien dengan MRSA penting dilakukan untuk mengoptimalkan penggunaan dan mengendalikan resistensi antibiotik. Tinjauan pustaka ini mengkaji efektivitas antibiotik pada pasien dengan MRSA. Tinjauan ini mengeksplorasi hasil penelitian sebelumnya dari PubMed sebagai sumber pustaka dan diagram alir PRISMA sebagai protokol proses pemilihan artikel. Delapan penelitian tentang evaluasi efektivitas penggunaan antibiotik pada pasien dengan MRSA pada berbagai kondisi klinis, seperti infeksi luka tanpa komplikasi, selulitis dan tanpa luka, *drainage* atau abses purulen, infeksi cSSSI oleh MRSA, infeksi yang disebabkan oleh bakteremia MRSA, dan infeksi nosokomial oleh MRSA. Kesimpulannya, efektivitas antibiotik pada pasien infeksi MRSA bergantung pada kondisi klinis masing-masing pasien. Oleh karenanya, penggunaan antibiotik disesuaikan berdasarkan jenis infeksi dan efektivitas antibiotik. Terapi kombinasi direkomendasikan untuk pasien MRSA mengingat kemampuannya yang mengancam jiwa.

*corresponding author: musdalifaas@mail.ugm.ac.id

INTRODUCTION

The Minister of Health of the Republic of Indonesia reported that infectious diseases are still becoming a public health problems. Antibiotics play an important against infectious diseases. However, inappropriate use of antibiotics and inadequate prevention of the infection cause antimicrobial resistance (AMR). Antimicrobial resistance occurs when germs such as bacteria and fungi do not die but grow and can defeat drugs designed to kill these germs, making them difficult and sometimes impossible to treat. Recently, the AMR has become a global health problem that threatens and affects the quality of health services.[2]

Staphylococcus aureus has long been well known as one of the most important bacteria that cause infectious diseases in humans. Although most infections caused by *S. aureus* are not fatal, it can cause serious infections such as bloodstream infections, pneumonia, or bone and joint infections. The infections can cause the emergence of Methicillin-resistant *Staphylococcus aureus* (MRSA) leading to resistance to more than 3 classes of antibiotics or multidrug-resistant organisms (MDRO) that makes its treatment more complex.[3-5] Methicillin-resistant *Staphylococcus aureus* resistance can occur in several different mechanisms such as changes in drug targets, enzymatic drug inactivation, and changes in drug accessibility.[4]

Epidemiological studies reported an MRSA prevalence of up to 14.69%.[6] The National Healthcare Safety Network (NHSN) demonstrated that antibiotic resistance in hospitalized patients in the United States reaches more than 2.8 million and causes more than 35,000 people deaths annually.[2] In Indonesia, it was reported the prevalence of MRSA reached 21%.[7] In Ethiopia, an increase in the prevalence of the emergence of resistant bacterial strains due to the inappropriate antibiotic use was reported. This resistant bacteria caused an increase in mortality, morbidity and problems related to health costs.[8]

This article review, we evaluated the effectiveness of antibiotics in patients with MRSA based on studies conducted in the last 10 years.

MATERIAL AND METHODS

This literature review was conducted using primary literature sources from the PubMed database with a search keyword of “antibiotics” and “MRSA”. All articles were selected based on the inclusion and exclusion criteria. The inclusion criteria were free full text available, articles from type randomized controlled trial, and articles published in the last 10 years. The exclusion criteria were review articles, and articles did not the research objectives. Among 398 articles were obtained from the searching, 106 articles were filtered based on inclusion criteria, and only 8 studies were included in qualitative synthesis. he PRISMA flowchart as a guide for the article selection process was used (FIGURE 1).

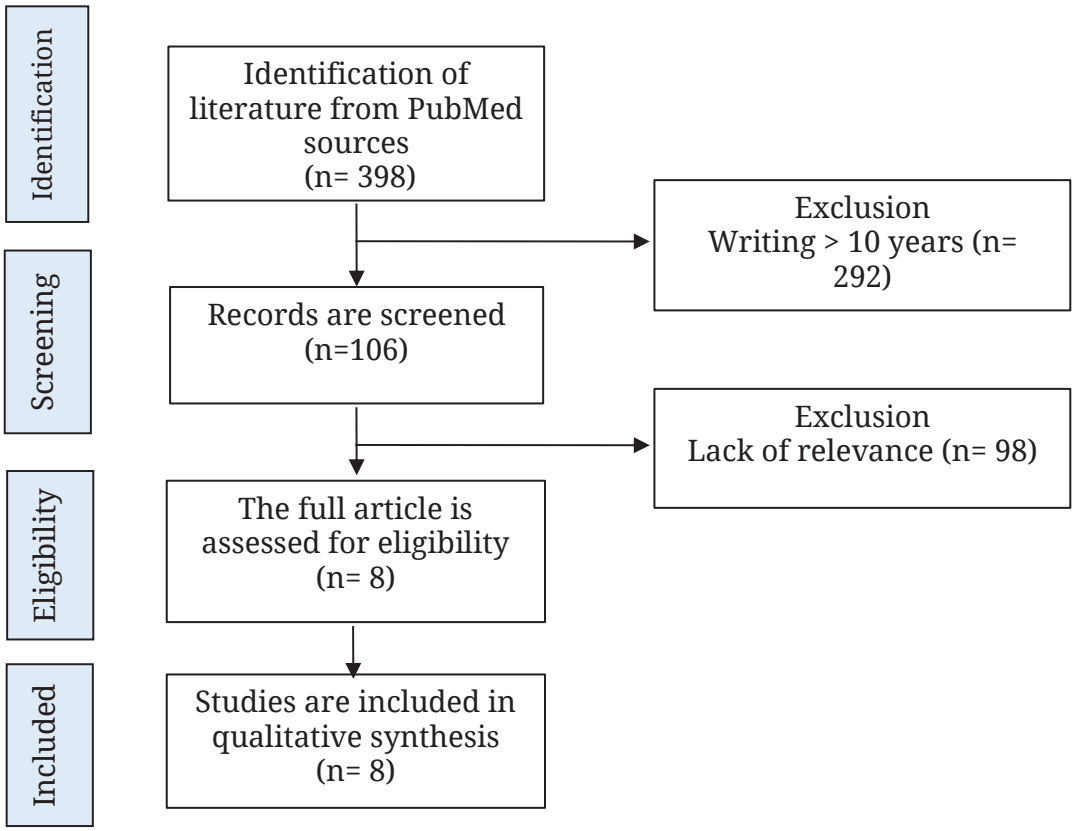

FIGURE 1. Search terms and publication selection process (PRISMA flowchart).

RESULTS

Among 398 articles identified and screened, only 8 articles were evaluated and discussed in this review (TABLE 1).

TABLE 1. Evaluation of antibiotic use in MRSA patients.

References	Methods	Subject	Diagnosed	Therapy	Result
Paul *et al.*[9]	Parallel, open label, randomized controlled trial	Adults	Severe infections caused by MRSA	TMP-SMX vs. vancomycin	91 (36%) of 252 patients had bacteremia. TMP-SMX (51/135, 38%) versus vancomycin (32/117, 27%) did not significantly differ in treatment failure (RR=1.38; 95%CI: 0.96 - 1.99). Nevertheless, the non-inferiority criterion was not met TMP-SMX; the AD was 10.4% (95%CI: 1.2 - 21.5%). The RR for bacteremia patients ranged from 0.91 to 2.16, with a value of 1.40. TMP-SMX was substantially linked to treatment failure in a multivariable logistic regression analysis [aOR=2.00 (1.09 - 3.65)]. 30-d mortality was 32/252 (13%), with no discernible variation between the arms. Among the patients with bacteremia, 9/50 (18%) and 14/41 (34%) who were treated with vancomycin and TMP-SMX respectively died [RR= 1.90 (0.92 to 3.93)].
Geriak *et al.*[10]	Open-label, randomized clinical trial	Adults	MRSA bacteremia	Daptomycin + ceftaroline vs. vancomicyn or daptomycin	The median duration of bacteremia of each group was 3 d. Significant difference in hospital mortality rate between combination therapy [0% (0/17)] and monotherapy [26% (6/23)] was reported (p= 0.029). In-hospital mortality for patients with an admission IL-10 concentration of less than 5 pg/mL was 25% (1/4) in the monotherapy group and 0% (0/3) in the combination group (p= 1.0). In-hospital mortality was 0% (0/14) in the combination therapy group and 26% (5/19) in the monotherapy group for an IL-10 levels of >5 pg/mL (p= 0.057).
Tong *at al.*[11]	Open-label, randomized clinical trial	Adults	MRSA bacteremia	Standard therapy (IV. vancomycin or daptomycin) plus an anti staphylococcal β-lactam (IV. flucloxacillin, cloxacillin, or cefazolin) vs. standard therapy alone	345 (98%) of the 352 randomly assigned patients finished the trial. 59 (35%) patients receiving combination therapy and 68 (39%) patients receiving standard therapy achieved the primary endpoint (AD=−4.2%; 95% CI:14.3% to 6.0%). In 7 of 9 predetermined secondary endpoints, there was no discernible variation. In the combination therapy versus standard therapy groups, there was a difference of 4.5% (95% CI:−3.7% - 12.7%) in all-cause 90-d mortality between 35 (21%) and 28 (16%); 19 of 166 (11%) vs. 35 of 172 (20%) had persistent bacteremia at day 5 (AD=−8.9%; 95% CI: −16.6% - −1.2%); and 34 of 145 (23%) versus 9 of 145 (6%) (AD: 17.2%; 95% CI: 9.3%-25.2%).

Note: MRSA: Methicillin-resistant *Staphylococcus aureus*; TMP-SMX: trimethoprim-sulfamethoxazole; AD: absolute difference.

TABLE 1. Evaluation of antibiotic use in MRSA patients (cont.)

References	Methods	Subject	Diagnosed	Therapy	Result
Pujol *at al.*[12]	A randomized (1:1) phase 3 superiority, open-label, and parallel group clinical trial	Adults	MRSA bacteremia	Daptomycin plus fosfomycin vs. daptomycin alone	55 of the 167 randomly assigned patients finished the trial and were evaluated for the main outcome. 40 of 74 patients who received daptomycin plus fosfomycin and 34 of 8 patients who received daptomycin alone reported success with their treatment at 6 wk following the end of therapy (54.1% vs. 42.0%; RR=1.29; 95%CI:0.93–1.8; p=.135). Daptomycin plus fosfomycin was linked, at 6 wk, to a lower incidence of complicated bacterial infections (16.2% vs. 32.1%; p=0.022) and microbiologic failure (0 vs. 9 patients; p=0.003). Of the 74 patients (17.6%) who received daptomycin + fosfomycin again, 4 patients (4.9%) who received daptomycin alone experienced adverse events that resulted in stopping their treatment (p=0.018).
Talan *et al.*[13]	A multicenter, double-blind, randomized trial	Adult patients	Uncomplicated wound infection	Clindamycin + TMP-SMX	Among specimens, 25.7% of *S. aureus* was susceptible to methicillin and 5.0% of streptococci. 187 of 203 (92.1%) clindamycin-treated and 182 of 198 (91.9%) TMP-SMX-treated, the wound infection was resolved after 7–14 d (AD= 0.2%; 95%CI:-5.8%-6.2%; p>0.05). At 7–14 d (1.5% vs. 6.6%; AD:-5.1%; 95%CI:-9.4% - -0.8%) and 6–8 wk after treatment (2.0% vs. 7.1%; AD:-5.1%; 95%CI:-9.7% - -0.6%). The clindamycin group had a significantly lower rate of recurrence. Although they tended to favor clindamycin, other secondary outcomes were statistically similar between groups. Rates of adverse events were comparable.
Moran *et al.*[14]	Multicenter, double-blind, randomized superiority trial	Outpatients > 12 yr.	Cellulitis and no wound, purulent drainage, or abscess	Cephalexin plus TMP - SMX vs. cephalexin plus placebo	Out of 500 randomly assigned subjects, 496 (99%) were included in the per-protocol analysis and 411 (82.2%) in the modified intention-to-treat analysis. The erythema's median length was 13.0 cm, and width was 10.0 cm. 182 (83.5%) of 218 subjects in the cephalexin + TMP-SMX group and 165 (85.5%) of 193 participants in the cephalexin group had clinical cure in the per-protocol population (AD:-2.0%; 95%CI:-9.7%-5.7%;p=0.50). 189 (76.2%) subjects in the cephalexin + TMP-SMX group and 171 (69.0%) subjects in the cephalexin group had clinical cure in the modified intention-to-treat population (AD:7.3%; 95% CI:-1.0%-15.5%; p=0.07). No significant difference between groups in the rates of adverse events or secondary outcomes after 7 to 9 wk, such as overnight hospitalization, recurrent skin infections, and similar infections in household contacts.

Note: MRSA: Methicillin-resistant *Staphylococcus aureus*; TMP-SMX: trimethoprim-sulfamethoxazole; AD: absolute difference.

TABLE 1. Evaluation of antibiotic use in MRSA patients (cont.)

References	Methods	Subject	Diagnosed	Therapy	Result
Kauf *et al.*[15]	An open-label, pragmatic, randomized	Patients must be at least 18 years old with SSSI complications	Complicated skin and skin structure infection (cSSSI)	Daptomicin and vancomicyn	Between-cohort differences in IRLOS, total LOS, and total inpatient cost were not observed. Hospital LOS was responsible for 85.9% of the overall hospitalization expenses, while drug costs accounted for 6.4%. On treatment day 2 and 3, daptomycin exhibited a nonsignificant trend toward a greater clinical success rate than vancomycin. Vancomycin was linked to a decreased chance of day 2 clinical success in the multivariate analyses (OR= 0.498, 95%CI:0.249 - 0.997; p< 0.05).
Equils *et al.*[16]	A double-blind, randomized, multi-center	Patients with DM	Pneumonia nosokomial	Linezolid vs vancomicyn	Out of 448 patients who were enrolled, 183 (40.8%) had DM; 87 (47.5%) patients were prescribed linezolid, and 96 (52.5%) were given vancomycin. For both treatment groups, baseline demographic and clinical characteristics were comparable. Microbiological success rates were 41.1% with vancomycin and 58.9% with linezolid at EOS, whereas clinical success rates were 576.6% with linezolid and 39.3% with vancomycin. The study drug's adverse effects and mortality rates among patients with diabetes were comparable across treatment groups. Overall, day 28 mortality rates for patients with diabetes were higher than those without the disease (23.5 vs. 14.7%; RD = 8.8%; 95% CI:1.4-16.3).

Note: MRSA: Methicillin-resistant *Staphylococcus aureus*; TMP-SMX: trimethoprim-sulfamethoxazole; AD: absolute difference.

DISCUSSION

Methicillin-resistant *Staphylococcus aureus* has been reported as a serious threat with various factors taken into consideration, including prevalence, affecting health services in the community, increasing the incidence of resistance, difficulty in treating, and transmission which is also difficult to prevent, causing increased death rates. The spread of MRSA has been detected throughout the world, and is an endemic disease in some large hospitals.[3,10,17] In this review, we included 8 studies that reviewed the evaluation of the effectiveness of antibiotic use in MRSA patients with various clinical conditions, such as uncomplicated wound infections, cellulitis and no wound, purulent drainage or abscess, cSSSI infections caused by MRSA, infections caused by MRSA bacteremia and nosocomial infections caused by MRSA.

An open-label, parallel, randomized controlled trial was carried out on adults who had severe MRSA infections and were responsive to vancomycin, TMP-SMX, and both. Excluded patients included those with meningitis, prolonged neutropenia, chronic hemodialysis, and left-sided endocarditis. For a minimum of 7 d and then as directed, TMP-SMX 320 mg/1600 mg twice daily versus vancomycin 1 g twice daily. The trial comprised 252 patients, of which 91 (36%) developed bacteremia. Trimethoprim-sulfamethoxazole (51/135, 38%) versus vancomycin (32/117, 27%) did not significantly differ in treatment failure (RR=1.38; 95%CI: 0.96 - 1.99) was observed. Nevertheless, the non-inferiority criterion was not met by TMP-SMX (AD=10.4%; 95%CI: −1.2% to 21.5%). The RR for bacteremia patients ranged from 0.91 to 2.16, with a value of 1.40. Trimethoprim-sulfamethoxazole was substantially linked to treatment failure in a multivariable logistic regression analysis [aOR=2.00; (1.09-3.65)]. The 30-day death rate was 32/252 (13%), with no discernible variation between the arms. Among the bacteremia patients, 9/50 (18%) and 14/41 (34%) who received vancomycin and TMP-SMX treatments, respectively, died [RR=1.90; (0.92 - 3.93)]. In conclusion, in high-dose TMP-SMX did not prove to be non-inferior to vancomycin for treating severe infection. For those suffering from bacteremia, the distinction was especially noticeable.[18]

The Infectious Diseases Society of America (IDSA) suggested vancomycin or daptomycin as the initial line of treatment for MRSA bacteremia in 2011.[12] Combination therapy is advised because up to 50% of treatment failures are linked to unfavorable outcomes, such as higher mortality. Furthermore, data indicate that severe MRSA respiratory infections might not respond well to vancomycin monotherapy, necessitating the addition of another antibiotic to maximize its efficacy.[13] In contrast to standard monotherapy treatment using vancomycin or daptomycin, the initial therapy with daptomycin in combination with ceftaroline was associated with a reduction in in-hospital mortality. According to a study that attempted to demonstrate the use of these antibiotics in combination with a β-lactam in patients with MRSA bacteremia. This is corroborated by experimental data, which demonstrates that β-lactams have a synergistic effect with peptides in endogenous cationic defense against MRSA, reduce cross-linking in the cell wall, increase access of daptomycin or vancomycin to cell membranes, and increase activation of the NLRP3 inflammasome and interleukin-1- (IL-1-) in bacterial clearance caused by changes in peptidoglycan synthesized by MRSA. Larger prospective studies are required to ascertain the role of combination therapy, particularly with beta-lactams, which are more effective in treating MRSA bacteremia by using biomarkers, such as IL-10, as a tool, given the high potential for nosocomial infections with a very high rate of treatment failure. Possibility of risk stratification when giving combination therapy to high-risk patients.[14]

A total of 352 hospitalized people with MRSA bacteremia participated in an open-label, randomized clinical research that was carried out at 27 hospital sites across 4 countries between August 2015 and July 2018. The last day of the follow-up was October 23, 2018. Randomized participants were assigned to receive either normal therapy (n = 174) plus an antistaphylococcal β-lactam (intravenous cefazolin, cloxacillin, or flucloxacillin) or standard therapy alone (n = 178). Normal therapy included intravenous vancomycin or daptomycin.

The treating professionals decided on the whole length of therapy, and the β-lactam was given for 7 d. For safety reasons, the data and safety monitoring board recommended ending the research early before 440 individuals were enrolled. Among 345 (98%) of the 352 patients who were randomly assigned [age =62.2 ± 17.7 yr; 121 women (34.4%)] finished the trial. A total 59 (35%) patients receiving combination therapy and 68 (39%) patients receiving conventional therapy achieved the primary objective (AD=−4.2%; 95% CI: −14.3% - 6.0%). There was no discernible change in 7 of the 9 prespecified secondary outcomes. In the combination therapy versus standard therapy groups, there was a difference of 4.5% (95% CI, −3.7% to 12.7%) in all-cause 90-day mortality between 35 (21%) and 28 (16%); 19 of 166 (11%) vs 35 of 172 (20%) had persistent bacteremia at day 5 (AD=−8.9%; 95% CI, −16.6% - −1.2%); and 34 of 145 (23%) vs 9 of 145 (6%) (AD=17.2%; 95% CI: 9.3% -25.2%). Additionally, among patients who were receiving dialysis at baseline, 34 of 166 (11%) and 9 of 145 (6%) had AKI. Antistaphylococcal β-lactams, when added to standard antibiotic therapy with vancomycin or daptomycin, did not significantly improve the primary composite end point of treatment failure, relapse, mortality, or persistent bacteremia in patients with MRSA bacteremia. When interpreting the results, one should take into account the early termination of the trial due to safety concerns, as well as the possibility that the study was underpowered to detect clinically significant differences in favor of the intervention.[9]

In 18 Spanish hospitals, a randomized (1:1) phase 3 superiority, open-label, parallel-group clinical trial including adult inpatients with MRSA bacteremia was carried out. Patients were randomized to receive either 10 mg/kg IV daptomycin daily or 10 mg/kg IV daptomycin daily plus 2 g of IV fosfomycin every 6 h. After 6 wk following the conclusion of therapy, treatment success was the main goal. Among 55 of the 167 randomly assigned patients finished the trial and were evaluated for the main outcome. Among 40 of the 74 patients who received daptomycin plus fosfomycin and 34 of the 81 patients who received daptomycin alone reported success with their treatment at 6 wk following the end of therapy (54.1% vs. 42.0%; RR=1.29; 95%CI: 0.93–1.8; p=0.135). Daptomycin plus fosfomycin was linked, at 6 wk, to a lower incidence of complicated bacterial infections (16.2% vs. 32.1%; p=0.022) and microbiologic failure (0 vs. 9 patients; p=0.003). Among 13 of 74 patients (17.6%) receiving daptomycin plus fosfomycin and 4 of 81 patients (4.9%) receiving daptomycin alone experienced adverse events that resulted in treatment discontinuation (p=0.018). Although the rate of treatment success with daptomycin plus fosfomycin was 12% higher than with daptomycin alone, the difference was not statistically significant. Although this combination of antibiotics avoided microbiological failure and complicated bacteremia, it was more frequently linked to unfavorable outcomes.[15]

A randomized trial comparing TMP-SMX, a relatively inexpensive and non-patented oral antibiotic, and clindamycin. The majority of simple wound infections are caused by MRSA, which typically retains in vitro activity against CA-MRSA, according to the study's findings. When oral clindamycin 300 mg is administered 4 x daily, it can effectively promote wound healing 7 to 14 d after treatment, with an efficacy of up to 92.1%. The TMP-SMX 320 mg/1600 mg administered twice a day can achieve 91.9% (AD=0.2%; 95% CI: −5.8% - 6.2%; p>0.05). Comparable levels of adverse effects were observed in the gastrointestinal tract, with TMP-SMX exhibiting a side effect percentage of

32.8% and clindamycin 37.3%.[17] The purpose of this superior trial was to investigate the hypothesis that patients treated with clindamycin would heal wound infections more quickly than patients treated with TMP-SMX. This theory is supported by clinical observational data, experimental results, and theoretical results that show TMP-SMX to be less effective.[16]

Multicenter, double-blind, randomized superiority trial conducted from April 2009 to June 2012 among outpatients over 12 y.o. with cellulitis who did not have a wound, purulent drainage, or abscess in five US Emergency Departments. At the time of enrollment, all participants underwent soft tissue ultrasonography to rule out abscesses. The last update came in August of 2012. For 7 d (n = 248), either cephalexin plus TMP-SMX (320 mg/1600 mg twice daily) or cephalexin plus placebo (n = 248) was administered. Out of 500 randomly assigned subjects, 496 (99%) were included in the per-protocol analysis and 411 (82.2%) in the modified intention-to-treat analysis [median age, 40 yr (range, 15-78 yr); 58.4% male, and 10.9% with diabetes]. The erythema measured 10.0 cm in width and 13.0 cm in length on average. Among 182 (83.5%) of 218 participants in the cephalexin plus TMP-SMX group and 165 (85.5%) of 193 participants in the cephalexin group experienced clinical cure in the per-protocol population (AD=−2.0%; 95% CI: −9.7% - 5.7%; p=).50). Among 189 (76.2%) of 248 participants in the cephalexin plus TMP-SMX group and 171 (69.0%) of 248 participants in the cephalexin group experienced clinical cure in the modified intention-to-treat population (AD=7.3%; 95% CI:−1.0% - 15.5%; p=0.07). There was no significant difference in the rates of between-group adverse events or secondary outcomes after 7 to 9 wk, such as overnight hospitalization, recurrent skin infections, and similar infections in household contacts. In the per-protocol analysis, using cephalexin plus trimethoprim-sulfamethoxazole instead of cephalexin alone did not lead to higher rates of clinical resolution of cellulitis among patients with uncomplicated cellulitis. Further investigation might be necessary, though, given that the modified intention-to-treat analysis's imprecise results included a clinically significant difference that favored cephalexin plus TMP-SMX.[19]

A pragmatic clinical trial comparing vancomycin and daptomycin in the management of community-selected surgical site infections (cSSSI) caused by MRSA aimed to investigate clinical efficacy as well as health costs. The trial results showed that both vancomycin and daptomycin demonstrated clinical success in terms of improvement and cure, though not significantly. However, logistic regression analysis indicated that vancomycin treatment was associated with a higher likelihood of clinical success within 2 d (OR= 0.498; 95%CI:0.249–0.997; p=0.049). Further research is necessary, but this study also suggested the possibility of a long-term drop in the length of stay (LOS) as patients are released from the hospital, suggesting a quicker rate of clinical improvement after daptomycin.[20]

For the treatment of nosocomial MRSA, the American Thoracic Society and the Infectious Diseases Society of America (IDSA) also suggest vancomycin or linezolid as suitable antibiotics. This is consistent with studies conducted on diabetic patients who had MRSA; those treated with linezolid had a much higher cure rate than those treated with vancomycin. At the end of treatment (EOT),

82.4% of diabetes patients receiving linezolid versus 64.8% receiving vancomycin had clinical success [95%CI: 17.6%, (4.5 - 30.7)]. Similarly, at EOT, 57.0% of diabetic patients treated with vancomycin and 83.8% of diabetic patients treated with linezolid showed microbiological success [95% CI: 26.8% (13.7 - 39.9)]. Among 57.6% of diabetes patients treated with linezolid and 39.3% of patients treated with vancomycin had clinical success at the end of study (EOS) visit [95% CI: 18.2% (2.6 - 33.9)]; 58.9% of diabetes patients treated with linezolid and 41.1% of patients treated with vancomycin had microbiological success at the EOS visit [95% CI: 17.8% (2.6, 33.0)]. In diabetic patients, 28-day mortality was higher than in non-diabetics regardless of treatment, but it was similar in those who received linezolid and vancomycin. Growing older and having received dialysis for chronic kidney disease are two additional factors linked to the higher death rate among patients with diabetes mellitus.[21]

The ability of MRSA to spread deadly diseases has led to MRSA being classified as a "priority pathogen" by the WHO. MRSA infections can affect the joints, bones, lungs, heart, and blood vessels. Treatment becomes more difficult when treating MRSA infections because it can negate the effects of many commonly used antibiotics. According to WHO study, patients with MRSA infections have a 64% higher mortality rate than patients with other infections. An estimated 35,000 deaths in the US are caused by antibiotic-resistant infections each year.[11] Consequently, it's critical to assess how well antibiotics work for MRSA patients. In an attempt to guarantee that patients receive the appropriate antibiotics at the appropriate time and for the appropriate length of time, this review evaluates several antibiotics that are commonly used in patients with MRSA. This will improve health services, lower the incidence of antibiotic resistance, save costs, and decrease the number of deaths.[22]

CONCLUSION

In conclusion, the effectiveness of antibiotics in patients with MRSA infection depends on the clinical condition of each patient. The use of antibiotics is adjusted based on the type of infection and the efficacy of the antibiotics against the infection. Combination therapy is recommended rather than monotherapy for MRSA patients considering its life-threatening ability.

ACKNOWLEDGEMENT

Authors would like to thank our colleagues for their suggestion and commend during preparing the review articles.

REFERENCES

1. Kementerian Kesehatan Republik Indonesia. Permenkes nomor 28 tahun 2021 tentang pedoman penggunaan antibiotik. Jakarta: Kementerian Kesehatan Republik Indonesia, 2021. https://peraturan.go.id/id/permenkes-no-28-tahun-2021
2. Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States 2019 - Google Search [Internet]. 2019 [cited 2023 Jan 27].
3. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, *et al.* Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infect Dis 2018; 18(3):318-27.
4. Vestergaard M, Frees D, Ingmer H. Antibiotic resistance and the mRSA problem. Microbiol Spect 2019 22;

7(2):GPP3-0057-2018.
https://doi.org/10.1128/microbiolspec.GPP3-0057-2018

5. Kementerian Kesehatan Republik Indonesia. Permenkes nomor 8 tahun 2015 tentang program pengendalian resistensi antimikroba di Rumah Sakit. Jakarta: Kementerian Kesehatan Republik Indonesia, 2015. https://peraturan.go.id/id/permenkes-no-8-tahun-2015
6. Hasanpour AH, Sepidarkish M, Mollalo A, Ardekani A, Almukhtar M, Mechaal A, *et al.* The global prevalence of Methicillin-resistant *Staphylococcus aureus* colonization in residents of elderly care centers: a systematic review and meta-analysis. Antimicrob Resis Infec Control 2023; 12(1):4. https://doi.org/10.1186/s13756-023-01210-6
7. Dahesihdewi A, Dewi YP, Sugianli AK, Parwati I. Surveilans bakteri resistan multi obat dan kepekaannya terhadap antibiotik di rumah sakit Indonesia tahun 2018. [Laporan]. Jakarta: Perhimpunan Dokter Spesialis Patologi Klinik dan Laboratorium Indonesia, 2019.
8. Melese A, Genet C, Andualem T. Prevalence of vancomycin resistant enterococci (VRE) in Ethiopia: a systematic review and meta-analysis. BioMed Central Infect Dis 2020; 20(1):124. https://doi.org/10.1186/s12879-020-4833-2
9. Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, *et al.* Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by Meticillin resistant *Staphylococcus aureus*: randomised controlled trial. Br Med J 2015; 350:h2219. https://doi.org/10.1136/bmj.h2219
10. Geriak M, Haddad F, Rizvi K, Rose W, Kullar R, LaPlante K, *et al.* Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of Methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 2019; 63(5):e02483-18. https://doi.org/10.1128/AAC.02483-18
11. Tong SYC, Lye DC, Yahav D, Sud A, Robinson JO, Nelson J, *et al.* Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. JAMA 2020; 323(6):527-37. https://doi.org/10.1001/jama.2020.0103
12. Pujol M, Miró JM, Shaw E, Aguado JM, San-Juan R, Puig-Asensio M, *et al.* Daptomycin plus fosfomycin versus daptomycin alone for Methicillin-resistant *Staphylococcus aureus* bacteremia and rndocarditis: a randomized clinical trial. Clin Infect Dis 2021; 72(9):1517-25. https://doi.og/ 10.1093/cid/ciaa1081
13. Talan DA, Lovecchio F, Abrahamian FM, Karras DJ, Steele MT, Rothman RE, *et al.* A randomized trial of clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated wound infection. Clin Infect Dis 2016; 62(12):1505-13. https://doi.org/10.1093/cid/ciw177
14. Moran GJ, Krishnadasan A, Mower WR, Abrahamian FM, LoVecchio F, Steele MT, *et al.* Effect of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone on clinical cure of uncomplicated cellulitis: a randomized clinical trial. JAMA 2017; 317(20):2088-96. https://doi.org/10.1001/jama.2017.5653
15. Kauf TL, McKinnon P, Corey GR, Bedolla J, Riska PF, Sims M, *et al.* An open-label, pragmatic, randomized controlled clinical trial to evaluate the comparative effectiveness of daptomycin versus vancomycin for the treatment of complicated skin and skin structure infection. BioMed Central Infect Dis 2015; 15:503. https://doi.org/10.1186/s12879-015-1261-9
16. Equils O, da Costa C, Wible M, Lipsky BA. The effect of diabetes mellitus on outcomes of patients with

nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*: data from a prospective double-blind clinical trial comparing treatment with linezolid versus vancomycin. BioMed Central Infect Dis 2016; 16(1):476. https://doi.org/10.1186/s12879-016-1779-5

17. Turner NA, Sharma-Kuinkel BK, Maskarinec SA, Eichenberger EM, Shah PP, Carugati M, *et al.* Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. Nat Rev Microbiol 2019; 17(4):203-18. https://doi.org/10.1038/s41579-018-0147-4
18. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, *et al.* Clinical practice guidelines by the infectious diseases society of america for the treatment of Methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis 2011; 52(3):285-92. https://doi.org/10.1093/cid/cir034
19. Randolph AG, Xu R, Novak T, Newhams MM, Bubeck Wardenburg J, Weiss SL, *et al.* Vancomycin monotherapy may be insufficient to treat Methicillin-resistant *Staphylococcus aureus* coinfection in children with influenza-related critical illness. Clin Infect Dis 2019; 68(3):365-72.
20. Williams DJ, Cooper WO, Kaltenbach LA, Dudley JA, Kirschke DL, Jones TF, *et al.* Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft-tissue infections. Pediatrics 2011; 128(3):e479-487. https://doi.org/10.1542/peds.2010-3681
21. Nandhini P, Kumar P, Mickymaray S, Alothaim AS, Somasundaram J, Rajan M. Recent developments in Methicillin-resistant *Staphylococcus aureus* (MRSA) treatment: a review. Antibiotics 2022; 11(5):606. https://doi.org/10.3390/antibiotics11050606
22. Boswihi SS, Udo EE. Methicillin-resistant *Staphylococcus aureus*: an update on the epidemiology, treatment options and infection control. Curr Med Res Pract 2018; 8(1):18-24. https://doi.org/10.1016/j.cmrp.2018.01.001