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Systematic Review: A Comparison between Vancomycin and Daptomycin for Sepsis Infection Antibiotic Therapy

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Abstract

BACKGROUND: Sepsis is a dangerous condition that threatens life because of immune system dysregulation caused by an infection resulting in organ failure. One of the most common resistant strain bacteria that can cause sepsis is Methicillin-resistant Staphylococcus aureus (MRSA). Vancomycin is the first-line therapy for treating sepsis infection caused by MRSA, but recently there have been some MRSA strains that are resistant to vancomycin therapy.

AIM: This study aimed to review comparison between vancomycin and daptomycin for sepsis infection antibiotics therapy.

MATERIALS AND METHODS: This research was a systematic review using three databases such as PubMed, ProQuest, and ScienceDirect. The journal articles included in this study were about randomized controlled trial (RCT) studies published from 2011 to 2020.

RESULTS: This research included seven RCT studies, but none of them discuss the usage of daptomycin for sepsis treatment caused by MRSA. They discuss more the effect of dose, method of administration, and side effects of vancomycin therapy in relation to the outcome of the patient.

CONCLUSIONS: Because of the lack of RCT articles that conducted experiments of daptomycin usage for sepsis treatment caused by MRSA infection, this research could not compare the effectiveness between vancomycin and daptomycin. However, from some case reports included in this research, there was evidence that the usage of daptomycin base after vancomycin treatment failure will cause another treatment failure.

Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction caused by immune system dysregulation after infection [1]. Based on the data from the World Health Organization (WHO) in 2018, the prevalence of sepsis is 30 million cases per year, which leads to 6 million deaths per year globally. Most sepsis cases around the world emerge from low to middle economic outcome countries [2], [3].

One of the most frequent bacteria with antibiotic resistance that can cause sepsis is Methicillin-resistant *Staphylococcus aureus* (MRSA) [4]. Globally, the mean prevalence of MRSA infection is 17.4% from all kinds of infection. In the USA, MRSA infected 31.8/100,000 populations, and 75% of infections resulting in bacteremia that can develop into sepsis [5], [6]. The WHO stated that MRSA is one of the high-priority bacteria for new antibiotics research and development [7].

Based on the IDSA guideline in 2020, the first-line therapy for sepsis is vancomycin or daptomycin [8]. However, recently, some MRSA strains were found resistant to vancomycin [9], [10]. Casapao *et al*. (2013) also found a strain that is sensitive to vancomycin therapy during the microbiology sensitivity test becomes resistant to *in vivo*. The threat of antibiotic resistance makes a review needed to assess the effectiveness of vancomycin for sepsis first-line therapy compared to daptomycin [9]. This study aimed to review comparison between vancomycin and daptomycin for sepsis infection antibiotics therapy.

Materials and Methods

Study design

This review was reported using the “Preferred Reporting Items for Systematic Reviews and Meta-Analysis” guideline and written using the “Synthesis without Meta-Analysis” method. This systematic review was designed to answer the question of whether there is a different result between the treatment with vancomycin and daptomycin in patients with sepsis infection. This

Table 1: Summary of included studies

First Author, Year	Research location	Study type	Sample population	Antibiotics treatment	Total patients	Sepsis patient	Patients receiving vancomycin/ daptomycin	Mortality	Failure of treatment	Mean Jadad score
Sundalic *et al*., 2020	Croatia	Prospective single center open-label Randomized controlled trial	Patient aged≥18 years old, with resistance strain Gram-positive bacterial infection from blood culture	Vancomycin	74	11	24	4	–	2.5
Paul *et al*., 2015	Israel	Multicenter open label randomized controlled trial	All patient suspected or infected with MRSA	Vancomycin	252	91	117	13	32	2
Emonet *et al*., 2016	Switzerland	Single-center open parallel Randomized controlled trial	Patient aged≥18 years old, with positive culture of Gram-positive bacteria	Vancomycin	89	33	35	15 (from all research patient)	33 (from all research patient)	2.5
Niederman *et al*., 2014	USA, Asia, Europa, Latin Americans	Phase IV, double-blind, randomized, comparator-controlled, multicenter trial	–	Vancomycin	448	35	224	–	–	2.5
Fowler *et al*., 2020	11 countries (79.3% from the USA)	Randomized, double blind, placebo-controlled, superiority design	Patient aged≥18 years old	Vancomycin Daptomycin Vancomycin+Exebacase Daptomycin+Exebacase	45 71 	13 17 	13 3 21 5	8 8 	– – 	4
Berthaud *et al*., 2019	Paris	Open-label 1:1 randomized controlled trial	Patients aged 3–17 years old	Vancomycin	99	8	99	–	–	3
Chytra *et al*., 2012	Czech Republic	Single center, prospective, randomized, open label comparative study	Patient aged≥18 years old	Meropenem+Vancomycin	240	214	12	36 (from all research patient)	45	2.5

MRSA: Methicillin-resistant *Staphylococcus aureus*.

question includes the information of population (patient with sepsis caused by MRSA), intervention (vancomycin or daptomycin), and outcomes (mortality).

Eligibility criteria

The included studies for this review were following several criteria, including randomized controlled trial (RCT), English language articles, using vancomycin or daptomycin as treatment, and investigating sepsis patients caused by MRSA infection. The study was excluded if it was a non-randomized control trial, did not use vancomycin or daptomycin, and had an inappropriate population. In addition, duplicate publications, observational studies, review studies, and case reports were excluded from the study.

Search strategy

The included studies for this systematic review were collected from three online databases including PubMed, ProQuest, and ScienceDirect published between 2011 and 2020 in the English language. The keywords used for this systematic review were “sepsis,” “shock septic,” “MRSA,” “vancomycin,” and “daptomycin.” These keywords were utilized in combination to search all these databases for relevant literature.

Study selection

Two authors were independently screening the collected articles. Any disagreement was resolved by discussion. The inclusion criteria were according to population, interventions, comparators, and outcomes, that is, the population of patients with MRSA, intervention, and comparison of daptomycin or linezolid, and the outcome of mortality.

Data extraction and quality assessment

The data from the selected studies were extracted by two independent authors independently. Any disagreement was resolved by discussion to reach a consensus. The collected data included the author’s last name, year of study, location of study, the number of participants, type of treatment, and mortality outcome. The critical appraisal used in this review was Jadad Scoring.

Results

Figure 1 shows the process of selecting relevant studies. The seven studies were included in this systematic review with a total of 1316 patients. The characteristics of the studies are presented in Table 1. All studies were published from 2010 to 2020 and were of randomized control trial designs. Two studies were conducted in multination and five studies in a single nation, including Croatia, Israel, Swiss, France, and the Czech Republic. The sample size of included studies ranges from 45 to 448 participants. Four studies only used vancomycin treatment; two studies used a

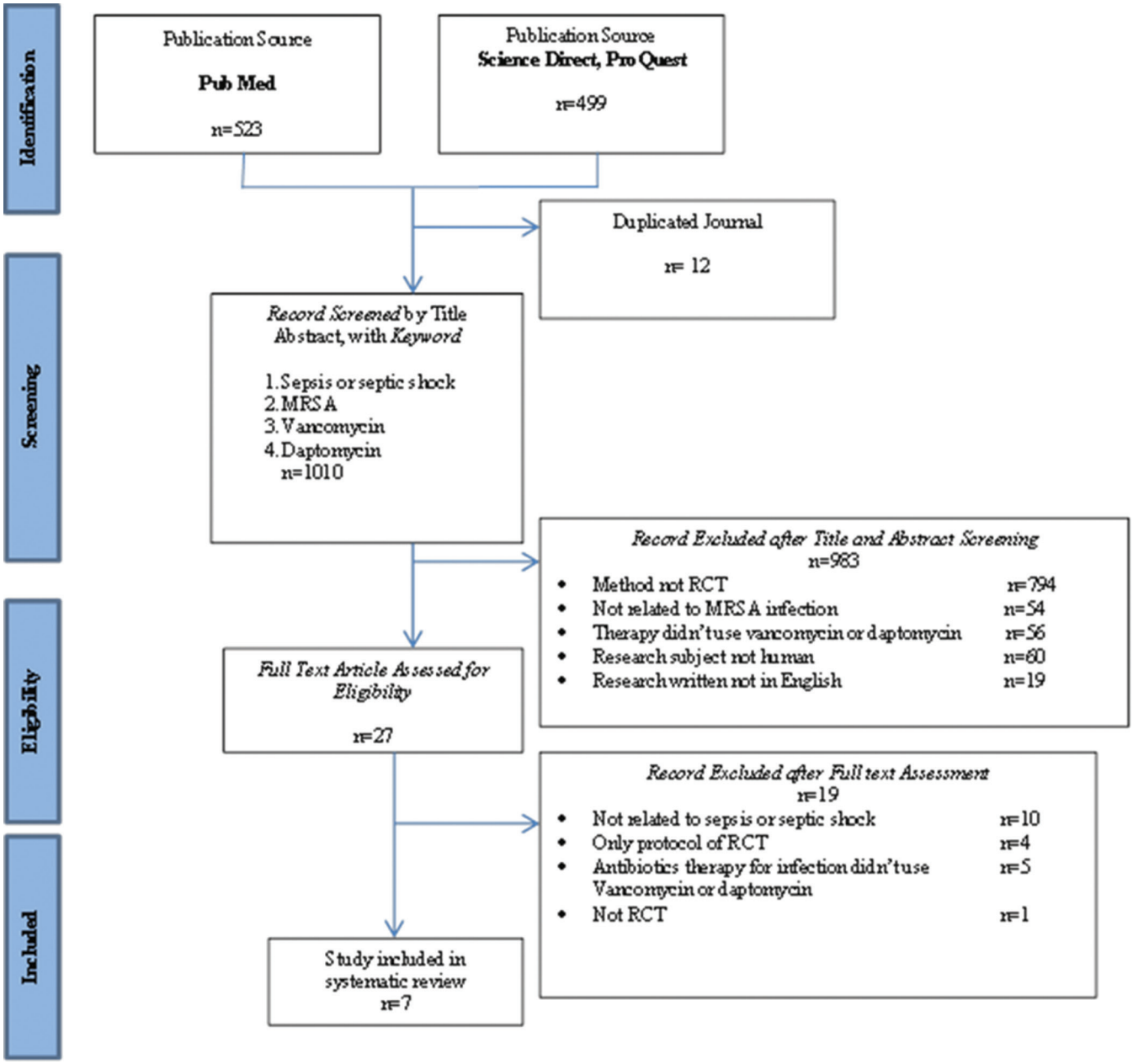

Figure 1: Flow diagram of the research procedure

combination of vancomycin and daptomycin, and the other used vancomycin plus meropenem as the treatment. Patient mortality was included in five studies with the number of deaths ranging from 4 to 36 while two studies did not show the number of deaths.

Most of the journals included in this review were open-label RCT, except for single double-blind RCT studies.

Discussion

In this systematic review, the difference in the effectiveness between vancomycin and daptomycin for sepsis caused by MRSA could not be compared since there was a lack of RCT studies found in databases that directly compared the use of vancomycin and daptomycin. Most RCT used vancomycin as the primary therapy [11], [12], [13], [14], [15], [16]. Although daptomycin has been included in the guideline for bloodstream infection caused by MRSA and has better efficacy than vancomycin, there is still a lack of RCT studies using daptomycin for sepsis treatment [8], [17], [18], [19]. In this systematic review, the use of daptomycin was only found in one RCT and was not used as the primary or comparison treatment in the research [19].

Although there was a lack of RCT about the daptomycin usage for sepsis treatment, there are some case reports about daptomycin use found during journal preview in this systematic review. Based on the compilation of 26 case reports between 2011 and 2012,

the failure of the first-line therapy using vancomycin 101 will result in the futility of daptomycin therapy. Most of the futilities occur when the minimum inhibitory concentration of vancomycin needed is greater than one. However, the combination of daptomycin and cefazoline will offer a successful therapy [20].

The mortality rate of sepsis patients caused by MRSA infection based on the journal articles included in this systematic review was 11.1–50%, and the failure rate of vancomycin therapy was 18.8–27.4% [12], [16], [21]. The mortality rate of sepsis patients caused by MRSA lies between 20% and 30%. Most of the studies included in this systematic review showed better outcomes of vancomycin therapies except for one study from America [21], [22]. These outcomes could have resulted from the difference in the prevalence of MRSA bacteria included in vancomycin-resistant *S. aureus* (VRSA), vancomycin intermediate *S. aureus* (VISA), or heterogeneous VISA (hVISA) between America and another continent. In America, the prevalence of VRSA, VISA, or hVISA is 3.6% while in Asia and Europe, the prevalence is 1.2% and 1.1%, respectively [23].

Many factors contribute to the failure of vancomycin therapy. Some of them correlate with the serum concentration of vancomycin during medication. Based on the guideline, the target vancomycin serum concentration is 15–20 mg/l. Low vancomycin serum concentration during treatment of <10 mg/l is associated with the presence of vancomycin-resistant strain bacteria [24]. Patients with serum vancomycin concordant to the target of area under the curve/minimum inhibitory concentration >400 in 24 h will likely have a 53% lower mortality rate and a 61% lower therapy failure rate [25].

From the data collected in this systematic review that presented in Table 2, the attainment of the target vancomycin serum concentration is still low. Sundalic *et al*. (2020) suggest only five out of 24 patients reach target vancomycin serum in 24 h while Paul *et al*. (2015) show that the median of vancomycin serum concentration in 117 patients is only 14.9 mg/l [11], [12]. Low vancomycin serum concentration during treatment is probably caused by an increase in the excretion rate in sepsis patients. In severe disorders like sepsis, the body volume distribution will be very high, which leads to escalation in the drug excretion rate [26]. On the other hand, Berthaud *et al*. (2019) show that altered vancomycin dose using Bayesian methods could increase the rate of patients achieving the target vancomycin serum concentration [15].

One of the side effects caused by vancomycin use is the emergence of renal damage because of vancomycin nephrotoxic properties [27]. The independent factor correlated with renal failure is the reach of vancomycin serum concentration of ≥15 mg/l while the target vancomycin serum treatment is 15–20 mg/l [24], [28], [29], [30], [31]. This problem shows the dilemma of sepsis or septic shock medication. It is caused by the increase in renal damage because of the disorder and medication. Apart from the increase in renal injury, the failure in renal function during sepsis or septic shock medication leads to an escalation of expenditure cost of approximately $52,257 [14].

Vancomycin can be combined with another antimicrobial treatment to tackle antibiotics resistance.

Table 2: Impact of Vancomycin usage during therapy

First Author, Year	Duration of Therapy	Vancomycin serum concentration	AKI/Kidney failure cases	Other founding
Sundalic *et al*., 2020	15–32.5 days	• Only five patients reached the concentration target of 15–20 mg/L in 12 h • 17 patients reached the target concentration of 15–20 mg/L in 72 h	Eight patients from all research sample	–
Paul *et al*., 2015	11–28 days	10.4–21 (median 14.9) From 97 patients whose serum vancomycin concentrations were measured, only 80 patients reached the target of>10 mg/L	–	–
Emonet *et al*., 2016	15–36 days (definitive antibiotics administration in 5 hours after detection)	–	–	Bacteriology examination with PCR shows faster the result compared to standard examination (3.9 vs. 25.4 h), but earlier administration of specific therapy does not affect the patient's mortality
	11.3–30.3 days (definitive antibiotics administration in 25.5 h after detection)	–	–	
Niederman *et al*., 2014	23.6 days (mean)	–	34 of 224 patients receiving vancomycin develop kidney failure	Patients who developed kidney failure from the vancomycin therapy spent $52,257, compared to those who did not develop kidney failure spending $29,923
Fowler *et al*., 2020	31.3 days (mean) (Antibiotics only)	–	–	
	36.6 days (mean) (antibiotics+Exebacase)	–	–	Additional therapy with Exebacase produced a better result of 42.8% compared to the antibiotics-only therapy
Berthaud *et al*., 2019	–	AUC 0–24/MIC>400 and AUC 0–24/MIC<800=34; Reach the target concentration of 20–40 mg/liter=27 (Bayesian dose)	–	Compared to standard dosing, dosing using The bayesian calculation provides significant results in achieving the target serum vancomycin concentration in 24 h
	–	AUC 0–24/MIC>400 and AUC 0–24/MIC<800=24; reaching the target concentration of 20–40 mg/l=16 (normal dose)	–	
Chytra *et al*., 2012	18–39 days (infusion)	–	–	Antibiotics administration via infusion or bolus produced a clinically insignificant result, but infusion showed a higher efficacy level of antimicrobial therapy
	14–42 days (bolus)	–	–	

AKI: Acute kidney injury, PCR: Polymerase chain reaction, AUC: Area under the curve, MIC: Minimum inhibitory concentration.

One of the drugs that can be used in combination with vancomycin is Exebacase, which is an anti-staphylococcal lysin [32], [33]. Exebacase is an antimicrobial drug that is not in the antibiotics class. This drug acts as peptidoglycan hydroxylase that synergically works with antibiotics to destroys biofilm produced by bacteria and decrease the rate of bacteria resistance to antibiotics [32], [33], [34], [35]. Fowler *et al*. (2020) found that Exebacase combined with vancomycin or daptomycin will increase the effectivity of therapy up to 42.8%, compared to a medication using vancomycin or daptomycin only [21].

Conclusions

Because of the lack of RCT journal articles about the experiment of daptomycin usage for sepsis treatment caused by MRSA infection, this research cannot compare the effectiveness between vancomycin and daptomycin. However, from some case reports included in this research, there is evidence that the usage of daptomycin base after vancomycin treatment failure will cause another treatment failure. Based on the data collected from several RCT included, the usage of vancomycin for sepsis therapy caused by MRSA infection is still viable although several factors affect the effectiveness of the therapy.

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Declarations

This manuscript is based on original work and has not been published in whole or part, in any printed or electronic media, or is under consideration of publication in any printed or electronic media other than as the abstract of conference proceedings.

Authors' Contributions

All authors contributed equally to the literature search and data analysis.

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