Original Article
The use of vancomycin in the treatment of adult patients with methicillin-resistant Staphylococcus aureus (MRSA) infection: a survey in a tertiary hospital in China

Jing Tang, Jiali Hu*, Lei Kang*, Zhengjun Deng, Jiaofen Wu, Jiaqian Pan

*Department of Clinical Pharmacy, Shanghai First People's Hospital, Shanghai Jiao Tong University, Shanghai 201620, PR China. *Equal contributors.*

Abstract: Background: Vancomycin is frequently used in the treatment of methicillin-resistant Staphylococcus aureus (MRSA). Objectives: To determine MRSA infection status and the use of vancomycin in its treatment at a teaching hospital in China. Methods: We retrospectively reviewed 140 cases of MRSA infection that were treated from January 2013 to October 2014. We analyzed the etiology of MRSA infection and the use of vancomycin in these cases. Results: MRSA infection mainly occurred in elderly patients concomitant with a variety of diseases, which incidence was more in men than women. More cases of MRSA infection were encountered in the ICU than in other departments. The positive culture results for MRSA were obtained in the sputum (38.57%), pharyngeal swab (19.29%), blood (5.71%), and wound secretion (11.43%) samples. The MRSA patients were sensitive to vancomycin, with the minimum inhibitory concentration (MIC) being 1 μg/mL in 53.80% of the cases and 2 μg/mL in 44.10% of the cases, respectively. Among the 35 (25%) cases treated with vancomycin, 23 were cured, while 3 died and 7 (20%) were considered as an unreasonable application. Conclusions: MRSA infection mainly appeared in patients admitted to the ICU. The MIC of vancomycin had a tendency to increase gradually.

Keywords: Vancomycin, MRSA, infection

Introduction

Staphylococcus aureus is one of the most common pathogens causing pyogenic infection in humans: it can cause local purulent infection, pneumonia, pseudomembranous colitis, pericarditis, and even general systemic infection, such as sepsis and bacteremia [1]. In particular, methicillin-resistant Staphylococcus aureus (MRSA) causes a serious problem of global hospital infection, which is first manifested in the infection of nosocomial Gram-positive bacteria. In recent years, the incidence of global hospital infection has witnessed a significant increase [2]. In large, comprehensive hospitals of China, nearly 80% cases with Staphylococcus aureus infections tested positive for MRSA [3]. For instance, in 2005, the average incidence of MRSA was 53.9% in five teaching hospitals of China, but there was a significant difference in the incidence rates of MRSA in different regions (Shanghai, 79.5%; Beijing, 56.4%; Shenyang, 50.0%; Zhejiang, 35.0%; and Wuhan, 31.6%) [4]. In contrast, the incidence rates of MRSA infection are usually < 5% in European countries, such as Denmark, Finland, Sweden, and Iceland [5]. Because MRSA is a multidrug-resistant strain, there are tremendous difficulties in the treatment and prevention of MRSA infection in hospital. Ever since MRSA was identified in 1961, vancomycin has been the drug of choice in the treatment of MRSA infection. However, as vancomycin has been extensively used for treating MRSA infection, some MRSA isolates have developed reduced susceptibility to this drug: these MRSA isolates are termed vancomycin intermediate resistant Staphylococcus aureus (VISA) [6]. Therefore, we need to seriously review whether vancomycin must be still used for controlling MRSA infection. In this

study, we have conducted a retrospective analysis of 140 cases diagnosed with MRSA infection. These patients have visited our hospital from January 2013 to October 2014. The main objective of this study is to have a better understanding of MRSA hospital infection, including its etiology and the use of vancomycin drug in its treatment. Our results serve as guidelines for the rational use of vancomycin in the clinical prevention and treatment of MRSA infection.

Materials and methods

Collection of clinical data of patients

We used the hospital information system (HIS) to extract the hospital infection information from patients' medical records. We initially reviewed 147 patients with MRSA infection; these patients were treated in our hospital from January 2013 to October 2014. However, we excluded 7 cases due to missing medical information. We collected the complete clinical data to create a database for the 140 cases, which were included as study subjects in this study. The patients' archived information was reviewed and approved by the Institutional Review Board (IRB) of our hospital.

Identification of bacteria and drug sensitivity testing

The bacterial culture was prepared in bacterial culture dishes; automatic bacteria identification and drug sensitivity of this culture was determined using VITEK 2 Compact analysis system (Biomérieux Diagnostics, France). For bacteria identification and drug sensitivity testing, the bacterial culture was also analyzed using the Walkaway automatic bacteria identification instrument (Siemens Ag Fwb, the Federal Republic of Deutschland). According to the CLSL (Clinical and Laboratory Standards Institute, CLSI) M100-S23 standard, MRSA infection was confirmed when the MIC value of Staphylococcus aureus of > 2 μg/mL for methicillin. When the MIC values of vancomycin were in the following ranges: ≤ 2 μg/mL, 4-8 μg/mL, ≥ 16 μg/mL, we defined the following drug sensitivity levels: sensitive, intermediary, and resistant.

Evaluation of vancomycin usage

The defined daily dose (DDD) and drug utilization index (DUI) were considered as the evaluation indices for vancomycin. DDD was defined as the total amount of drugs used: greater the DDD value, greater would be the clinical use of this drug. DUI was calculated by dividing the DDD with the actual duration for which the medication was consumed (in days). If the DUI > 1.0, the actual clinical use daily dose of this drug was greater than DDD, indicating drug abuse. If the DUI was close to 1.0, then the medication was used in a reasonable manner [7].

Evaluation of clinical efficacy

According to the Antibacterial Drug Treatment Guidelines established by the National Health and Family Planning Commission of the People's Republic of China, the clinical efficacy of a drug was classified into four grades as follows: Grade 1, Cure: no symptoms or signs; normal or negative results in laboratory tests and etiological examination (e.g., pathogen culture); Grade 2, Effective: clinical conditions improved markedly; abnormal results for 1 out of 4 items of laboratory tests; Grade 3, Progression: condition improved slightly; and Grade 4, Failure: condition was either not improving or aggravating. Grades 1 and 2 (Cure and effective) were collectively referred to as "clinically effective".

Evaluation of efficacy based on bacteriological assay

The efficacy was divided into four grades as follows: Grade 1, Clear: negative for bacterial culture at the end of treatment; Grade 2, Not Clear: positive for bacterial culture at the end of treatment; Grade 3, Partially Clear: negative for 1 out of 2 or more pathogenic bacteria; and Grade 4, Replace: primary pathogen was eradicated, but a new pathogen was found at the end of treatment.

Statistical analysis

SPSS16.0 software (IBM, Armonk, NY, USA) was not only used to establish the database but also to conduct statistical analysis of the data.

Results

Characteristics of patients with MRSA infection

In total, 147 cases of MRSA infection were detected in our hospital in the period extending

Table 1. Age distributions of patients with MRSA

Age	Cases	Percentage (%)
0-1	15	10.71%
1~18	3	2.14%
19-30	14	10.00%
31-60	46	32.86%
61-90	62	44.29%
Total	140	100%

Table 2. Departmental distribution of patients with MRSA

Department	Cases	Percentage (%)
ICU	73	52.14%
Obstetrics and Gynecology	8	5.71%
Pediatrics	16	11.43%
Oncology	3	2.14%
Surgery	22	15.71%
Internal medicine	17	12.14%
Others	1	0.71%

from January 2013 to October 2014. Among these 147 cases, we excluded 7 cases from our current analysis due to missing data. Thus, we included 140 cases in this study. Among these 140 subjects, 84 (60%) were male while 56 (40%) were female. Their ages ranged from 6 days to 89 years (**Table 1**). In these 140 cases, any of the following cultures tested positive for MRSA: the sputum (38.57%), pharyngeal swab (19.29%), blood (5.71%), and wound secretion cultures (11.43%).

Distribution of clinical departments

As shown in **Table 2**, most cases were admitted to the ICU, although MRSA cases were also reported in other clinical departments.

Clinical use of vancomycin

Among the 140 cases with MRSA infection, 35 (25%) cases were treated with vancomycin. The total drug (vancomycin) amount of the 35 cases was 1049.50 g, with the DDDs being 524.75; the total days of medication were 577 days. Therefore, the resultant DUI was 0.91. In **Table 3**, we provided the detailed statistics for the use of vancomycin in 35 cases, including the doses, routes of administration, drug treatments, clinical efficacy, and adverse events.

Drugs combined with vancomycin

As shown in **Table 4**, vancomycin was administered along with other antibiotics to the 35 cases.

Empiric therapy (The use of antibiotics based on physicians' experience)

As doctors had to wait for considerable time for obtaining the drug sensitivity testing results, they decided to begin antibiotic therapy immediately and administered the medications based on their clinical experience. **Table 5** summarizes the results of empiric therapy in patients treated with vancomycin.

Rationality of vancomycin use

Among the 35 cases treated with vancomycin, there was irrational or improper use of vancomycin in seven patients. Among the seven patients, 2 were judged not to be suitable for use of vancomycin; 3 were not suitable for combined use of drugs; and 2 were not treated with proper course of treatment.

Discussion

Elderly patients (61 years and above) accounted for 44.29% of the total MRSA cases analyzed in this study. Elderly patients often have several complications and underlying diseases, leading to decreased immunity, metabolic disorder, and increased susceptibility to drug-resistant bacteria. Moreover, elderly patients are more susceptible to MRSA infection owing to various other factors, such as longer hospital stay, broad-spectrum antibiotics, and various iatrogenic factors. Hands are the most common mode of nosocomial MRSA transmission [8]. The major reason for hands-mediated transmission is that persons (healthcare provider, patients, or family members) do not wash hands after touching infected patients or contaminated objects. MRSA infection may also spread through various modes of air transmission, causing tracheotomy, large skin burns, and dermatitis. In addition, the nasal carriage of MRSA among medical staff is also a risk factor [9]. Therefore, the prevention of nosocomial MRSA infection needs concerted efforts by patients, family members, and healthcare personnel.

Table 3. Clinical use of vancomycin, outcome, and adverse events

Parameters	Category	Number of cases (%)
Dosage	2 g/d (1 g, bid)	26 (74.28%)
	< 2 g/d	8 (22.86%)
	> 2 g/d (1 g, q8 h)	1 (2.86%)
Treatment duration (days)	7-14	15 (42.86%)
	< 7	6 (17.14%)
	> 14	14 (40.00%)
Route of administration	ivgtt (intravenous drip)	35 (100.00%)
Clinical efficacy	Cure/Effect	27 (77.14%)
	Failure	8 (22.86%)
Adverse events	Renal dysfunction	8
	Liver dysfunction	3

Table 4. Classification of drugs combined with vancomycin

Different Drugs	Cases	Percentage
Vancomycin only	13	37.14%
Vancomycin plus Two Antibiotics	15	42.86%
Vancomycin plus More than two Antibiotics	7	20%

Table 5. Empiric antibiotic therapy for patients treated with vancomycin

Antibiotics	Cases	Percentage
β-lactams antibiotics	16	45.72%
Enzyme alkenes hydrocarbon antibiotics	2	5.71%
4-quinolones antibiotics	2	5.71%
Glycopeptide antibiotics	7	20.00%
No empirical antibiotics	8	22.86%

In this study, the sputum culture of most patients tested positive for MRSA, accounting for 38.57% of the cases. This is because MRSA itself can exist in the nasal cavity and the upper respiratory tract, but it does not cause a clinically relevant disease. Therefore, although most sputum samples tested positive for MRSA, the respiratory system may not be the system that is severely affected by MRSA infection. Only an experienced physician can provide correct diagnosis and clinical judgment, thereby minimizing the unnecessary use of excessive antibiotics in patients. Thus, an experienced physician can minimize the burden of medical expenses in patients.

In this survey, we found that 35 (25%) out of 140 MRSA patients were treated with vancomycin. Among these 35 cases, 27 cases (77.14%) showed clinical efficacy while three cases suc-cumbed to MRSA infection. Although the deaths of three MRSA patients might not be linked to an excessive use of antibiotics, the chances of their survival would have increased had their infection been controlled rapidly and effectively: physicians should have treated them before knowing the results of MRSA culture and drug sensitivity. In general, the chances of getting cured from the infection are higher when physicians immediately administer the empirical therapy of correct antibiotics. In this study, 35 cases were empirically treated with vancomycin, even before confirming the diagnosis of MRSA: the clinicians selected a broad spectrum of antibiotics, including β-lactam antibiotics, 4-quinolones, and Carbapenem.

Owing to the extensive use of Vancomycin, the MIC values of Vancomycin against MRSA have been increasing worldwide, leading to the emergence of VISA [10]. Although no report has claimed the incidence of VISA in general population of China, the MIC values of vancomycin against MRSA have increased in certain studies [11]. The effect of the treatment has been related to the MIC of Vancomycin: when MIC > 1 µg/mL, the failure rate of vancomycin treatment increases significantly [12]. So, the rational use of glycopeptide antibiotics can effectively decrease the drug resistance of MRSA. In our study, we did not come across excessive use of antibiotics in our hospital as the DUI was < 1, and the overall average daily dose was about 1.82 g below the DDD. We did not determine why the patients in our hospital were administered with a relatively low dose of vancomycin. However, we infer that patients with renal dysfunction and elderly patients might have been administered low doses of vancomycin.

The use of vancomycin for MRSA infection was justified in some of our patients. The combination therapy mainly included the combined regimen of vancomycin and carbapenems with other aminoglycoside drugs, which increase the risk of developing nephrotoxicity and ototoxicity. If combination therapy is needed to treat

MRSA infection, then the third generation cephalosporins should be administered [13]. According to Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), vancomycin can be used in the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children [14]. However, while treating pulmonary infection, vancomycin should not be administered for more than 21 days. For treating bloodstream infection, vancomycin should not be prescribed for more than 6 weeks. However, for treating bloodstream infection, vancomycin treatment must be provided for at least 2 weeks. In addition, if vancomycin is administered for a long duration of time, it may cause damage to liver and kidney [15].

MRSA infection accounts for 64% of all the hospital infection of Staphylococcus aureus and 40% of ICU infection of Staphylococcus aureus [16]. The incidence, mortality, and medical costs of MRSA infection are higher than those of methicillin sensitive Staphylococcus aureus (MSSA) infection [17]. Some reports suggest that the mortality of Staphylococcus aureus bacteremia is greater than 50% [18]. Therefore, MRSA infection must be diagnosed and treated in patients at an early stage; these patients must also be isolated to prevent an outbreak of MRSA in hospital.

Due to the extensive use of vancomycin, the MIC of vancomycin against MRSA is increasing every year [19]. The 2011 Guideline for Clinical Application of Antibiotics in China states that vancomycin is an antibiotic meant for special use. Vancomycin should only be used as the last line of defense against MRSA infection; this medication must be prescribed only after rationally evaluating its use in individual patients. It is necessary to monitor the blood concentration of vancomycin. Moreover, before adjusting the individual dosage regimen, physicians must take into consideration the results of drug sensitivity of MRSA. In addition, antibiotics and other drugs should also be used in accordance with their indications and adverse effects in order to avoid the overuse of antibiotics. This would also delay the occurrence of VISA in patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jing Tang, Department of Clinical Pharmacy, Shanghai First People's Hospital, Shanghai Jiao Tong University, No. 650 Xinsongjiang Road, Shanghai 201620, PR China. Tel: +862137798317; Fax: +862137798605; E-mail: angel_tj99@126.com; angel_tj99@163.com

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