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## Retrospective Study

**Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections**

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**Abstract****BACKGROUND**

Vancomycin and teicoplanin are both antibiotics that have significant antimicrobial effects on Gram-positive cocci.

**AIM**

To explore the value of teicoplanin combined with conventional (vancomycin only) anti-infective therapy for the treatment of methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* pulmonary infections.

**METHODS**

A total of 86 patients with methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis* pulmonary infections, treated in our hospital between January 2018 and February 2020, were assigned to the study and control groups using a random number table method, with 43 patients in each group. The control group received conventional treatment (vancomycin), and the study group received both teicoplanin and conventional treatment. The following indicators were assessed in both groups: the time required for symptom relief, treatment effectiveness, serum levels of inflammatory factors (procalcitonin, interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , C-reactive protein), clinical pulmonary infection scores before and after treatment, and the incidence of adverse reactions.

**RESULTS**

Patients in the study group were observed to have faster cough and expectoration resolution, white blood cell count normalization, body temperature normalization, and rales disappearance than patients in the control group (all  $P < 0.05$ );

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the total rate of effectiveness was 93.02% in the study group, higher than the 76.74% in the control group ( $P < 0.05$ ). The pre-treatment serum levels of procalcitonin, interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , and C-reactive protein as well as the clinical pulmonary infection scores were similar among the patients in both groups. However, the post-treatment serum levels of procalcitonin, interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , and C-reactive protein as well as the clinical pulmonary infection scores were significantly lower in the study group than in the control group ( $P < 0.05$ ). There was no significant difference in the incidence of adverse reactions between the groups.

## CONCLUSION

Compared with conventional (vancomycin only) therapy, teicoplanin and vancomycin combination therapy for patients with pulmonary methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis* infections can improve patient clinical symptoms, modulate serum inflammatory factor levels, and improve treatment efficacy, without increasing the risk of adverse reactions.

**Key Words:** Vancomycin; Teicoplanin; Methicillin-resistant *Staphylococcus aureus*; Methicillin-resistant *Staphylococcus epidermidis*; Lung infection

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**Core Tip:** Vancomycin and teicoplanin are both essential drugs in the clinical treatment of methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* lung infections and have significant antimicrobial effects on Gram-positive cocci. Here, we discuss the efficacy and safety of these two key antibiotics.

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## INTRODUCTION

Pulmonary infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) are common in our hospital. These infections are typically resistant to treatment with cefradine, oxacillin, or methicillin. In recent years, the incidence of these infections has been rising continuously, and they have become challenges that seriously threaten patients' lives, health, and prognoses[1-3].

Vancomycin and teicoplanin are important drugs in the clinical treatment of MRSA and MRSE lung infections and have significant antimicrobial effects on Gram-positive cocci. However, the overall efficacy of treatment with vancomycin alone is not good; increasing the dosage to ensure a therapeutic effect also increases the risk of adverse reactions, resulting in a significant limitation to its use as a single-drug treatment[4-6]. Teicoplanin is a novel glycopeptide antibacterial preparation for use in place of vancomycin. This novel drug has enhanced antibacterial activity against MRSA and MRSE due to the addition of fatty acid side chains to its chemical structure, which also increases its molecular mass and half-life, relative to vancomycin[7,8]. Additionally, teicoplanin has a longer dosing interval than vancomycin, which has increased its safety and reduced its risk of adverse events (*e.g.*, renal toxicity and Redman syndrome) compared with vancomycin[9,10].

Thus, we selected 86 patients with pulmonary MRSA or MRSE infections treated in our hospital and compared the treatment outcomes in patients receiving conventional antimicrobial treatment (vancomycin only) with those receiving treatment with vancomycin and teicoplanin.

## MATERIALS AND METHODS

### Patient population

Patients were eligible to participate in the study if they had pulmonary MRSA or MRSE infections confirmed by lung computed tomography, X-ray examination, and blood cultures, were less than 80 years of age, and agreed to demonstrate good compliance and cooperate throughout the study. Patients were excluded if they had mixed pulmonary infections caused by multiple drug-resistant bacteria species, evidence of immune system dysfunction, an expected survival time of less than 2 wk, kidney or other organ lesions, malignancies, allergies to the study medications, cardiovascular or cerebrovascular diseases, or if they failed to demonstrate compliance throughout the investigation. This study was approved by the ethics committee of our hospital.

### Treatment

Patients in both groups received routine interventions after hospitalization, including treatments to reduce expectoration and suppress coughing; supplemental oxygen was also provided. The control group received intravenous vancomycin (0.5 g in 250 mL of normal saline, every 8 h). Peak drug concentrations were measured after 3 d of treatment, and the dosage was adjusted to maintain 5–10 mg/L of vancomycin. Patients in the study group were similarly dosed with vancomycin and also received intravenous teicoplanin (0.4 g in 250 mL of normal saline, every 12 h for 3 d, then once per day for the duration of treatment). Both groups were treated for 7 d.

### Indicators

Both groups were monitored to determine the period of time from the beginning of treatment to symptom relief. The indicators of symptom relief were normalization of white blood count and body temperature and the disappearance of cough, expectoration, and rales. We also monitored the patients for lung lesion resolution (resolution of 90% of the lesions was scored as marked effectiveness; resolution of 50%–89% of the lesions was considered effective) using radiography. Thus, the total effectiveness rate was determined as the percentage of patients in each group demonstrating effective and markedly effective outcomes[11]. We also compared the baseline and post-treatment levels of serum inflammatory factors between the groups, including procalcitonin, interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , and C-reactive protein; we also assessed the pre- and post-treatment clinical pulmonary infection scores (CPISS). Serum levels of inflammatory markers were determined using appropriate enzyme-linked immunosorbent assays. Finally, the experience of adverse events during treatment was compared between the groups.

### Statistical analysis

All statistical analyses were performed using SPSS (version 22.0, SPSS, Chicago, IL, United States). A *P* value < 0.05 was considered statistically significant. Means were compared using *t*-tests, and qualitative data (percent values) were compared using the  $\chi^2$  test.

## RESULTS

A total of 86 patients with pulmonary MRSA or MRSE infections, treated in our hospital between January 2018 and February 2020, were randomly assigned (using a random number table) to the study and control groups; 43 patients were assigned to each group. The study group comprised 24 men and 19 women. At baseline, the average age of the participants in the study group was  $58.59 \pm 10.77$  (range: 46–71) years, and the average body mass index was  $22.19 \pm 3.07$  (range: 18.2–26.4) kg/m<sup>2</sup>. The average duration of their disease was  $6.05 \pm 2.13$  (range: 2–10) d. The comorbidities among this group included chronic obstructive pulmonary disease (*n* = 11), coronary heart disease (*n* = 2), cerebrovascular disease (*n* = 4), chronic bronchitis (*n* = 11), and other diseases (*n* = 2).

The control group included 26 men and 17 women, with an average age of  $60.07 \pm 11.35$  (range: 43–76) years and an average body mass index of  $21.95 \pm 3.23$  (range: 17.8–27.1) kg/m<sup>2</sup>. The average duration of disease in this group was  $5.89 \pm 2.32$  (range: 1–10 d). The comorbidities in this group included chronic obstructive pulmonary disease (*n* = 10), coronary heart disease (*n* = 4), cerebrovascular disease (*n* = 5), chronic

bronchitis ( $n = 9$ ), and other diseases ( $n = 4$ ). Based on these baseline data, there were no significant differences between the two groups.

### **Time to symptom relief**

In the study group, the routine blood test results returned to normal after treatment, with complete resolution of clinical symptoms. Post-treatment X-ray examinations also showed that  $> 90\%$  of the lung lesions resolved, indicating marked effectiveness. In the control group, the routine blood test results also returned to normal, the clinical symptoms improved significantly, and the post-treatment X-rays showed an effective rate of  $50\%–89\%$  for lung lesion resolution.

The study group demonstrated significantly faster cough and expectoration disappearance, white blood count normalization, body temperature normalization, and rales disappearance than the control group (all  $P < 0.05$ ; [Table 1](#)).

### **Treatment effect**

The total effective rate of the study group ( $93.02\%$ ) was higher than that of the control group ( $76.74\%$ ;  $P < 0.05$ ) ([Table 2](#)).

### **Serum inflammatory factors and CPISSs**

In the study group, the baseline serum levels of the inflammatory factors and the CPISSs were similar to those in the control group ([Table 3](#)). After treatment, the serum levels of the inflammatory factors and the CPISS scores were significantly lower than those in the control group ( $P < 0.05$ ; [Table 3](#)).

### **Adverse events**

There was no significant difference in the incidence of adverse events between the study ( $11.63\%$ ) and control ( $6.98\%$ ) groups ( $P > 0.05$ ), as shown in [Table 4](#).

## **DISCUSSION**

Pulmonary MRSA and MRSE infections are types of antimicrobial-resistant infections that are common in our hospital and are associated with shock, ventilator use, invasive surgeries, and anesthesia. Most patients with these infections experience some degree of dyspnea, fever, expectoration, and other manifestations[12,13]. Moreover, the incidence of pulmonary infections caused by MRSA and MRSE has continued to increase over recent years due to the increasing frequency of antibiotic misuse. The most effective way of treating these types of infections remains a research hotspot.

The drugs currently used to treat pulmonary infections are glycopeptide antibacterial agents, including the wide use of vancomycin, a drug that inhibits bacterial cell wall synthesis by stopping the synthesis of the cell wall glycopeptide polymerase[14]. Vancomycin has a significant antibacterial effect on Gram-positive bacteria, especially *Staphylococcus epidermidis* and *Staphylococcus aureus*. However, it also has a nephrotoxic effect on the patient. The administration frequency of this drug should be kept as low as possible, particularly in elderly patients and those with other severe illnesses, to reduce the drug's kidney toxicity[15].

Teicoplanin is another important drug used in the clinical treatment of pulmonary infections and is also a novel glycopeptide antibacterial agent. Compared with vancomycin, the peptide skeleton of teicoplanin contains additional fatty acid side chains, which have a  $90\%$  binding rate to serum albumin and high lipophilicity. This characteristic of this drug promotes the absorption of the drug by tissues and cells[16]. Sezai *et al*[17] used vancomycin and teicoplanin to treat patients with MRSA pulmonary infections and demonstrated complete bacterial clearance in  $87.80\%$  (a total effective rate of up to  $90.24\%$ ) of the patients in the test group, which was significantly higher than the  $68.29\%$  with complete clearance in the control group. The patients in the test group also demonstrated significantly lower post-treatment serum procalcitonin and C-reactive protein levels than before treatment. Ogawa *et al*[18] also confirmed that the application of high-dose teicoplanin can effectively downregulate the levels of inflammatory factors and improve bacterial clearance in patients with pulmonary MRSA infections.

Compared with our conventional (vancomycin only) treatment, treating pulmonary MRSA and MRSE infections with vancomycin and teicoplanin resulted in a higher total effective rate than for the conventional treatment. These results are consistent with the results of the above-mentioned studies. In addition, the time to symptom relief was shorter than in the control group, and the post-treatment CPISSs were lower

**Table 1 Average symptom relief time for patients treated with either vancomycin only or vancomycin and teicoplanin (mean  $\pm$  SD)**

	Vancomycin only	Vancomycin + teicoplanin	P value
Patients (n)	43	43	
Cough and expectoration resolution (d)	8.29 $\pm$ 2.15	6.12 $\pm$ 1.56	0.000
WBC normalization (d)	8.68 $\pm$ 2.44	6.77 $\pm$ 2.13	0.000
Body temperature normalization (d)	5.68 $\pm$ 1.18	4.07 $\pm$ 1.09	0.000
Rales resolution (d)	8.89 $\pm$ 2.02	6.64 $\pm$ 1.43	0.000

WBC: White blood cell count.

**Table 2 Treatment effects for patients treated with vancomycin (only) or vancomycin and teicoplanin, n (%)**

Group	Number of cases	Markedly effective	Effective	Ineffective	Total efficiency
Study group	43	26 (60.47)	14 (32.56)	3 (6.98)	40 (93.02)
Control group	43	18 (41.86)	15 (34.88)	10 (23.26)	33 (76.74)
$\chi^2$ value					4.441
P value					0.035

**Table 3 Inflammation marker levels in patients treated with vancomycin (only) or vancomycin and teicoplanin**

Group	Number of cases	PCT (ng/mL)	IL-1 $\beta$ (pg/mL)	TNF- $\alpha$ (pg/mL)	CRP (mg/L)	CPIS (point)
Before treatment						
Study group	43	0.86 $\pm$ 0.23	223.37 $\pm$ 36.25	139.74 $\pm$ 23.65	91.39 $\pm$ 10.68	7.69 $\pm$ 2.88
Control group	43	0.91 $\pm$ 0.20	219.29 $\pm$ 35.56	142.91 $\pm$ 20.88	89.24 $\pm$ 12.29	8.01 $\pm$ 3.04
t value		1.076	0.527	0.659	0.866	0.501
P value		0.285	0.600	0.512	0.389	0.618
After treatment						
Study group	43	0.28 $\pm$ 0.03	141.18 $\pm$ 18.62	41.46 $\pm$ 9.08	11.76 $\pm$ 4.43	2.19 $\pm$ 0.79
Control group	43	0.34 $\pm$ 0.05	163.53 $\pm$ 23.84	50.96 $\pm$ 10.35	18.25 $\pm$ 5.39	3.87 $\pm$ 1.01
t value		6.748	4.845	4.525	6.100	8.591
P value		0.000	0.000	0.000	0.000	0.000

CPIS: Clinical pulmonary infection score; CRP: C-reactive protein; IL-1 $\beta$ : Interleukin-1 $\beta$ ; PCT: Procalcitonin; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .**Table 4 Adverse events experienced by patients treated with vancomycin (only) or with vancomycin and teicoplanin, n (%)**

Group	Number of cases	Gastrointestinal reaction	Dizziness and headache	Vomiting and nausea	Total incidence
Study group	43	2 (4.65)	1 (2.33)	2 (4.65)	5 (11.63)
Control group	43	0 (0.00)	2 (4.65)	1 (2.33)	3 (6.98)
$\chi^2$ value					0.551
P value					0.458

than those in the control group. However, there was no significant difference in the incidence of adverse reactions between the two groups. This indicates that combining teicoplanin and vancomycin treatments in patients with pulmonary MRSA and MRSE infections can effectively improve the treatment effect, relative to the conventional treatment, while ensuring patient safety.

We believe that the additional benefit provided by teicoplanin can be explained as follows. The main antibacterial mechanism of teicoplanin is its ability to inhibit transglycosylation during bacterial cell wall synthesis, thereby damaging the integrity and strength of the cell wall. This results in bacterial growth inhibition and the ultimate killing of the bacteria. Teicoplanin demonstrates strong tissue penetration, high protein binding, and a long half-life. Therefore, even once-daily administration can maintain an ideal blood concentration and bioavailability[19]. Some studies also indicate that good lipophilic properties of teicoplanin facilitate drug penetration into tissues and cells. Thus, the drug effectively regulates the transfer of disaccharides and peptides required for cell wall mucins and stops cell wall biosynthesis, thereby promoting bacterial death[20]. The mechanism of action of teicoplanin is similar to that of other glycopeptide antibacterial agents, including its non-specific binding to the outer structure of peptide glycolipids and binding with the amino terminal of the aminoacyl D-alanyl-D-alanine in the bacterial cell wall. This inhibits the formation of the peptide glycolipid, glycogen transfer, and bacterial cell wall biosynthesis, inhibiting bacterial growth[21].

Furthermore, procalcitonin, interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , and C-reactive protein are indicators of the degree of inflammatory response in the body. Inflammation can increase the permeability of vascular endothelial cells, promote the exudation of numerous inflammatory substances from tissues, and aggravate the disease. In this study, the levels of these inflammatory indicators in the study group were significantly lower than in the control group after treatment. These results indicate that teicoplanin has high value in the treatment of pulmonary MRSA and MRSE infections in part because it downregulates the inflammatory response.

## CONCLUSION

Our study demonstrated that, compared to conventional therapy, the combined teicoplanin/vancomycin treatment of patients with pulmonary MRSA and MRSE infections results in improved clinical responses, regulates the levels of serum inflammatory factors, and improves the disease treatment effect, without increasing the risk of adverse events.

## ARTICLE HIGHLIGHTS

### Research background

Vancomycin and teicoplanin are important drugs in the clinical treatment of methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* lung infections.

### Research motivation

Single-drug treatment of lung infections is not effective.

### Research objectives

We want to compare the therapeutic effects of conventional antibacterial therapy (vancomycin only) and vancomycin plus teicoplanin.

### Research methods

We selected 86 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) or *Staphylococcus epidermidis* lung infections and divided them into a study group and a control group, with 43 cases in each group.

### Research results

The study group was more effective than the control group.

### Research conclusions

The combined teicoplanin/vancomycin treatment of patients with pulmonary methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* infections resulted in improved clinical responses.

**Research perspectives**

The combined application of antibacterial drugs increases the cure rate of the disease.

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