

—Case Report—

Long-term Treatment of Teicoplanin for Methicillin-resistant *Staphylococcus aureus* Sternal Osteomyelitis with Renal Impairment: A Case of High Teicoplanin Trough Levels Maintained by Therapeutic Drug Monitoring

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Teicoplanin, a glycopeptide antibiotic for methicillin-resistant *Staphylococcus aureus*, is recommended for therapeutic drug monitoring during treatment. Maintaining a high trough range of teicoplanin is also recommended for severe infectious disease. However, the optimal dose and interval of treatment for severe renal impairment is unknown. We report a 79-year-old man who received long-term teicoplanin treatment for methicillin-resistant *Staphylococcus aureus* bacteremia due to postoperative sternal osteomyelitis with renal impairment. Plasma teicoplanin trough levels were maintained at a high range (20–30 µg/mL). Although the patient required long-term teicoplanin treatment, a further decline in renal function was not observed, and blood culture remained negative after the start of treatment. Teicoplanin treatment that is maintained at a high trough level by therapeutic drug monitoring might be beneficial for severe methicillin-resistant *Staphylococcus aureus* infection accompanied by renal impairment.

Key words—teicoplanin; therapeutic drug monitoring; renal impairment; methicillin-resistant *Staphylococcus aureus*; bacteremia

INTRODUCTION

According to the results of nationwide surveillance of surgical site infection at 27 medical centers in Japan, *Staphylococcus aureus* and *Enterococcus faecalis* are the most common isolates. The rate of methicillin-resistant *S. aureus* (MRSA) among *S. aureus* is 72%.¹⁾

The first-line treatment of choice for MRSA infections is glycopeptide antibiotics, such as vancomycin and teicoplanin.²⁾ Although both of these glycopeptide drugs increase nephrotoxicity, teicoplanin causes less renal dysfunction than vancomycin.^{3,4)} However, hepatic dysfunction tends to occur more with teicoplanin than with vancomycin.³⁾

Therapeutic drug monitoring (TDM) is warranted to ensure the maintenance of optimal drug plasma concentrations and to minimize the risk of toxic effects of drugs, such as nephrotoxicity. Therefore,

implementation of TDM is recommended during treatment with glycopeptide antibiotics.^{5,6)} Although the initial loading and maintenance doses of teicoplanin for a creatinine clearance (Ccr) of 40–60 (mL/min) has been reported for renal impairment dosing,⁵⁾ an optimal dosing method for severe renal impairment has been not established (Ccr < 40 mL/min).

We report a patient with long-term teicoplanin treatment for MRSA bacteremia that developed from chronic postoperative wound infection and sternal osteomyelitis. The patient was also complicated by severe renal impairment.

Ethical Approval This work was approved by the Ethics Committee of University of the Ryukyus.

CASE DESCRIPTION

A 79-year-old male patient (61.8 kg) with combined valvular disease received aortic valve replacement in August 2013. After the operation, a chronic postoperative wound infection and sternal osteomye-

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Table 1. Drug Susceptibility of MRSA from Blood Culture on Day -33 of Teicoplanin Treatment

MRSA drug susceptibility		
MPIPC	≧4	R
PCG	≧16	R
IPM	≧8	R
AMPC/CVA	≧8	R
EM	≧8	R
CLDM	≧4	R
VCM	2	S
TEIC	2	S
ABK	≧1	S
LZD	1	S
DAP	2	—
LVFX	≧8	R

MPIPC: oxacillin, PCG: penicillin-G, IPM: imipenem, AMPC/CVA: amoxicillin/clavulanate, EM: erythromycin, CLDM: clindamycin, VCM: vancomycin, TEIC: teicoplanin, ABK: arbekacin, LZD: linezolid, DAP: daptomycin, LVFX: levofloxacin.

litis developed. MRSA was detected from wound cultures at least three times during treatment. The CLSI standards classified minimum inhibitory concentrations (MICs) of detected MRSA were 1–2 $\mu\text{g}/\text{mL}$ for vancomycin, ≤ 0.5 –2 $\mu\text{g}/\text{mL}$ for teicoplanin, 1 $\mu\text{g}/\text{mL}$ for linezolid, and 2–4 $\mu\text{g}/\text{mL}$ for daptomycin. On day -33 starting teicoplanin treatment, the patient developed a wound abscess, and was diagnosed with MRSA bacteremia because MRSA was detected in blood culture. The MICs of MRSA detected on day -33 are shown in Table 1. The value of Ccr from the Cockcroft-Gault equation (33 mL/min) was indicated that the patient had developed severe renal impairment. Therefore, linezolid 600 mg was administered every 12 h (q12 h) from days -33 to -1. On day -27, wound debridement was performed. Because the platelet count was less than 100000/ μL on days -3 to -1, linezolid was switched to teicoplanin treatment on day 1. The patient received five doses of 400 mg of teicoplanin q12 h as a loading dose (Fig. 1), and TDM was performed before the sixth teicoplanin administration. The teicoplanin plasma trough value was 14.3 $\mu\text{g}/\text{mL}$ at the first TDM on day 6. The target maintained range of teicoplanin trough level was set at 20–30 $\mu\text{g}/\text{mL}$. Subsequently, based on simulation analysis (teicoplanin simulation analysis was performed by teicoplanin TDM analysis support software; Sanofi K.K., Tokyo), we administered 400 mg of teicoplanin q12 h for two times as a re-loading dose on days 8 and 9. A 200 mg of teicoplanin q24 h

for maintenance dose was then administered after day 10. The second TDM was performed on day 19, and the teicoplanin trough level was maintained at the target range (24.9 $\mu\text{g}/\text{mL}$, half-life [$t_{1/2}$] β : 277 h) and treatment was continued. However, follow-up TDM on day 44 showed that the teicoplanin trough level had reached 40.5 $\mu\text{g}/\text{mL}$ ($t_{1/2}\beta$: 402 h). Therefore, teicoplanin administration was discontinued until it was reduced to the target trough range. An increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels was concomitantly observed (Fig. 1). This observation was assumed to be due to an adverse reaction of caspofungin. Therefore, administration of caspofungin was switched to fos-fluconazole. After switching drugs, the patient's hepatic function rapidly improved within 10 days. Based on the result of TDM on day 52, we decided to resume teicoplanin administration from day 63 and also set the dose of teicoplanin at 200 mg q48 h as a maintenance dose (dose interval was changed from day 77). Although trough sampling was not performed, the last TDM performed on day 79 showed that teicoplanin was maintained in the target range (29.2 $\mu\text{g}/\text{mL}$). Antibiotic treatment was eventually switched to oral administration of minocycline and rifampicin after day 103. During teicoplanin treatment of the patient, Ccr was maintained at almost 20–40 mL/min. No MRSA was detected from wound and blood cultures during teicoplanin treatment, and there was no further liver dysfunction after switching from caspofungin to fos-fluconazole administration. After switching to oral medication, MRSA was not detected from two sets of blood cultures on days 141 and 170.

DISCUSSION

A previous report showed that the proportion of MRSA isolates was elevated from 1986 and constituted approximately 60% of the total *S. aureus* strains isolated from 1990–2005.⁷⁾ Even today, the most common strain of *S. aureus* is MRSA,¹⁾ and the prevalence of MRSA infection among the strains of *S. aureus* was shown to be 45.5% at a general hospital in Japan.⁸⁾ The glycopeptide antibiotics teicoplanin and vancomycin are used to treat MRSA infections.⁵⁾ Because teicoplanin trough concentrations are closely related to clinical outcomes,⁹⁾ TDM and an initial loading procedure are recommended for maintaining an adequate trough concentration range.⁶⁾ In the

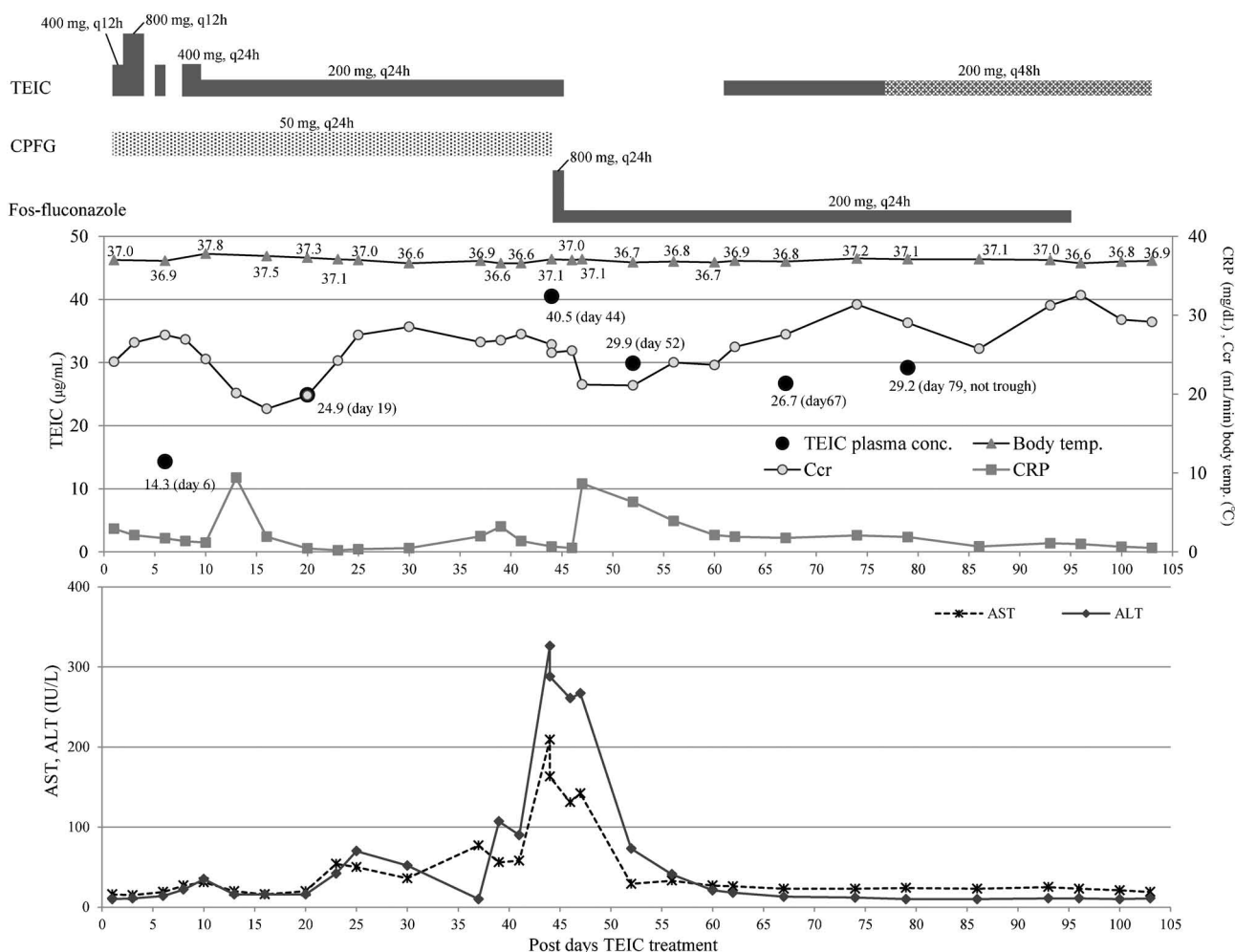


Fig. 1. Clinical Course of the Patient

Drugs and dosages for methicillin-resistant *Staphylococcus aureus* and fungus are shown (upper panel). The results of TDM of teicoplanin, changes in laboratory values, and body temperature are shown (middle and lower panels). TEIC: teicoplanin, CPFG: caspofungin, CRP: C-reactive protein, Ccr: creatinine clearance (calculated by the Cockcroft-Gault equation), AST: aspartate aminotransferase, ALT: alanine aminotransferase.

present case, 400 mg of teicoplanin was administered for q12 h as an initial loading dose on days 1 to 3. At TDM on day 6, the teicoplanin plasma trough level was 14.3 $\mu\text{g}/\text{mL}$. Generally, Clinician recommend that a teicoplanin trough level of $\geq 10 \mu\text{g}/\text{mL}$ should be achieved for treating the majority of infections.^{5,10,11} However, current recommendations suggest that teicoplanin trough levels should be maintained at $>20 \mu\text{g}/\text{mL}$ for severe infections.^{12,13} Therefore, we consider that a re-loading dose should be administered after the first TDM so that the teicoplanin trough level reaches the target range at the second TDM. In our study, 20–40 mL/min of Ccr was obtained after reaching teicoplanin trough levels $\geq 20 \mu\text{g}/\text{mL}$. Teicoplanin induced renal dysfunction has been reported in rats, as shown by the finding that blood urea nitrogen and serum creatinine levels, were

not significantly increased at a 10–30 mg/kg dose of teicoplanin.³ In the standard teicoplanin regimen, a trough levels 15–30 $\mu\text{g}/\text{mL}$ is difficult to achieve, even in patients with renal dysfunction.¹³ In the present case, although teicoplanin trough levels were high ($>40 \mu\text{g}/\text{mL}$), Ccr remained at 20–30 mL/min throughout teicoplanin administration above the target trough range. Therefore we consider that our recommended active loading dose and maintenance of teicoplanin at high trough levels ($\geq 20 \mu\text{g}/\text{mL}$) might be safe for renal impairment in patients with a Ccr of 20–40 mL/min. Additionally, after re-loading doses on days 8 and 9, the teicoplanin trough level was above the target range on day 44. This observation might be due to a steady state not being achieved on day 19 because the calculated $t_{1/2\beta}$ of day 44 (402 h) was more prolonged than that of day 19 (277 h).

Teicoplanin has an 88 to 182 h serum half-life in patients with normal renal function.⁵⁾ These observations suggest that the teicoplanin half-life could be substantially prolonged in patients with a Ccr of 20–40 mL/min. Therefore, implementation of TDM of teicoplanin in patients with severe renal impairment should be frequently performed to determine whether steady state has been reached and to calculate actual half-life. Additionally, software simulation can be useful to determine and assess the half-life. However, the calculated half-life of this case on day 19 was not actually, TDM practitioner should be alert to these pharmacokinetic characteristics.

Yoshida *et al.* reported that teicoplanin at a high dose (40–60 mg/kg) significantly increases AST and ALT levels from 0 to 8 h following teicoplanin administration to rats.³⁾ Hayakawa *et al.* also reported that glutamic oxaloacetic transaminase and glutamic pyruvic transaminase significantly increased as the trough levels of teicoplanin increased, with only slight renal dysfunction.¹⁴⁾ However, hepatic dysfunction as shown by an increase in AST (4–6%) and ALT levels (2–4%), has been reported as a major adverse reaction of caspofungin.^{15,16)} Although the present patient did not have further renal dysfunction during teicoplanin treatment, we observed impairment of hepatic function; AST and ALT levels were increased on days 40 to 45. AST and ALT levels rapidly improved after switching from caspofungin to fluconazole and discontinuation of teicoplanin. This finding might be due to an additive effect of the high teicoplanin trough level and caspofungin-induced hepatic dysfunction. Finally, MRSA was not detected in the patient during anti-MRSA treatment. This therapeutic effect could be due to teicoplanin as well as to preliminary administration of linezolid.

CONCLUSION

In summary, we report a case of long-term teicoplanin treatment with severe renal impairment. Findings from our case suggest that maintenance of a teicoplanin trough level at a high range controlled by TDM is useful and safe in the clinical situation, even in patients who have severe renal impairment.

Conflict of Interest The authors state that they have no conflict of interest.

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