Ineffectiveness of Daptomycin in the Treatment of Septic Pulmonary Emboli and Persistent Bacteremia Caused by Methicillin-resistant *Staphylococcus aureus*

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**Abstract**

A 73-year-old man with long-term food deprivation and total parenteral nutrition was diagnosed with septic pulmonary emboli (SPE) and a persistent bacteremia caused by central line-associated blood stream methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Although daptomycin (DAP) failed to treat the persistent bacteremia, linezolid successfully controlled it. DAP is inactivated by lung surfactant, and therefore, it should not be administered for lower respiratory infections. However, SPE caused by MRSA has been reported to be treatable with DAP since it is an infection of the lung parenchyma. We herein report the lack of effect of daptomycin in SPE treatment.

**Key words:** central line-associated blood stream infection, daptomycin, linezolid, methicillin-resistant *Staphylococcus aureus*, septic pulmonary emboli, suppurative thrombophlebitis

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**Introduction**

*Staphylococcus aureus* bacteremia (SAB) is not a benign condition; it results in significant morbidity and mortality, especially in patients in intensive care units (ICU) \((1, 2)\). The 30-day all-cause mortality rate and infection-related mortality rate of SAB are estimated to be approximately 20% \((3)\) and 13% \((4)\), respectively. Compared to methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) has been associated with a greater likelihood of persistent bacteremia \((5)\), and the mortality rates are reported to be significantly higher for MRSA than for MSSA bacteremic episodes \((6, 7)\). Therefore, the management of MRSA bacteremia patients poses a challenge.

To date, although various anti-MRSA drugs have been developed, for the treatment of MRSA bacteremia, vancomycin (VCM) remains the treatment of choice \((8)\). However, as numerous reports have shown an increased mortality rate with episodes of a high minimum inhibitory concentration (MIC), in 2006 the breakpoint of VCM against MRSA was lowered from a MIC of 4 μg/mL to 2 μg/mL \((9-15)\). Some consider that the MIC should still be lowered further \((16, 17)\). Therefore, the role of VCM in the treatment of MRSA bacteremia is expected to become more limited in the future.

Daptomycin (DAP), a newly created lipopeptide, is a bactericidal antibiotic active against MRSA and its clinical efficacy in treatment of MRSA infection has been widely proven to be as effective as VCM \((5, 18-21)\). According to recent guidelines, DAP is recommended as an alternative agent for VCM \((8)\). However, DAP is not suitable for the treatment of respiratory infection since the drug is inactivated by lung surfactant in alveolar tissue. Septic pulmonary emboli (SPE) is an infection of the pulmonary parenchyma, and consequently SPE caused by MRSA has been suggested to be treatable with DAP \((22)\). However, the previous study was only a small scale study; we feel that the clinical efficacy of DAP in the treatment of SPE thus still remains controversial and should be reassessed.

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Case Report

A 73-year-old man presenting with colicky abdominal pain was diagnosed with acute obstructive suppurative cholangitis and underwent endoscopic sphincterotomy. One week later, a computed tomography (CT) scan revealed pancreatitis, and a central venous catheter (CVC) for total parenteral nutrition (TPN) was inserted into his right femoral vein. Two weeks later, a follow-up CT scan showed a pancreatic pseudocyst, and the patient continued to receive TPN. After 2 weeks, a high fever and a high-grade inflammatory state developed. The CVC was removed and reintroduced into the right internal jugular vein with a suspected central line-associated blood-stream infection (CLABSI). However, the high fever persisted for another week, and a CT scan showed cavity-forming consolidations suggesting septic pulmonary emboli (SPE) in the peripheral regions of both lungs (arrow).

Two sets of initial blood cultures detected MRSA, and a decreased dose of vancomycin (VCM, 0.5 g every 12 h) was thus initiated due to his deteriorated renal function. His fever and high-grade inflammatory state persisted, therefore the CVC was removed. Nevertheless, MRSA continued to be detected in the blood culture (second sampling), and even after 5 days of VCM administration, bacteremia persisted (third sampling). MIC of VCM examined by Microscan Walkaway (SIEMENS, Germany) against the pathogen was found to be relatively high (2 μg/mL). The antibiotic treatment was switched to DAP [350 mg (6.4 mg/kg) every 24 h]. Antibiotic susceptibility testing was performed for DAP using calcium agar frozen plates (Eiken Co. Ltd., Tokyo, Japan), and the isolate was shown to be sensitive to DAP [MIC: 0.5 μg/mL (Table)]. However, MRSA bacteremia remained uncontrolled after 3 days of DAP treatment (fourth sampling), and one week later, the patient abruptly developed respiratory failure and was admitted to the ICU.

Soon thereafter, he was intubated because of respiratory failure. PaO₂/FiO₂ was less than 100 under ventilator support. Laboratory testing on the ICU admission showed a highly inflammatory state (white blood cell count of 14,600/mm³; C-reactive protein level of 19.3 mg/dL), and blood culture again detected MRSA (fifth sampling). The Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated to be 22 and 7, respectively. CT scan revealed right massive pleural effusion and bilateral ground glass opacity, thus indicating acute respiratory distress syndrome (ARDS), and enlarged lung cavities (Fig. 2A). The right pleural effusion was drained, and sampling of the fluid showed MRSA. Contrast enhanced CT (CECT) showed a thrombus from the right internal jugular vein to the brachiocephalic vein (Fig. 2B, C). The right internal jugular vein was considered completely obstructed by the thrombosis; blood flow was not detected by either the echogram or CECT. The pseudocyst in the pancreas remained unchanged. Trans-thoracic and trans-esophageal echocardiogram (TTE/TEE) did not show any evidence of infective endocarditis (IE). There were no cutaneous inflammatory findings indicating jugular vein supplicative thrombophlebitis (JVST) of the right internal jugular vein. A diagnostic puncture, per-
formed against the thrombus, revealed no purulent material and the bacterial culture was negative. Based on the clinical course and these findings, SPE was suspected to be the primary source of the persistent MRSA bacteremia and antibiotic treatment was switched to intravenous linezolid [LZD (600 mg every 12 h)]. After the switch, the pathogen was not cultured from the blood culture anymore and the persistent MRSA bacteremia was considered successfully controlled. However, the patient’s condition did not improve, and despite intensive care, eventually he died of respiratory failure approximately one month later.

An autopsy was performed with the permission of the family. His right internal jugular vein was obstructed by thrombus, but it was negative for any pathogenic organism. A precise examination of his heart valves did not reveal any findings related to IE. The lungs firmly adhered to the thoracic wall and some large cavities, thus indicating SPE to have formed inside. The pancreas showed necrotic changes with abscess formation that extended to the posterior mediastinum and bacterial culture obtained from his pancreas showed miscellaneous organisms, but not MRSA.

**Discussion**

Persistent bacteremia is reported to occur in from 6% to 38% of SAB episodes (23). Risk factors include the source of infection (i.e., uncontrolled intravascular infections such as IE, CLABSI, JVST, and mycotic aneurysm, abscess, the presence of prosthetic material, or vertebral osteomyelitis), pathogen phenotypes (hetero-resistance to VCM), or the content of antibiotic treatment. The median time to clearance is reported to be from 7 to 9 days (5, 24). The longer the bacteremia persists, the higher the likelihood of a metastatic infection, which can be as high as approximately 45% following more than 10 days of SAB (24). A larger case-controlled study showed that the mortality rates for persistent (more than 7 days) SAB were significantly higher than those of non-persistent controls [54.8% and 31.4%, respectively; p<0.01 (25)], and another study established persistent bacteremia as being an independent predictor of mortality [OR, 17.5; 95% CI, 1.5 to 212; p=0.024 (26)].

There have been many other reported predictors of higher mortality in patients with SAB; elderly age, being female, immunosuppression, comorbidities such as alcoholism, cirrhosis, congestive cardiac failure, malignancy, chronic renal failure requiring hemodialysis, the presence of these multiple comorbidities, functional status of daily living, higher score of Charlson weighted comorbidity index, and the presence of concomitant bacteriuria (23). The presence of sepsis or septic shock is closely associated with worse outcomes, with mortality rates ranging between 38% and 86% (27, 28). It was also reported that sepsis is a strong independent predictor of 30-day all-cause mortality [OR, 4.01; 95% CI, 2.34 to 6.87; p<0.001 (3)]. Moreover, the source of infection is
significantly related to the patient’s prognosis. SAB which is secondary to endovascular and lower respiratory infection can be categorized into the high-risk group, and in such case, the mortality rate is estimated to be approximately 30% (23, 29). Thus, the prognosis of the present patient was considered to be significantly lower based on his age and septic shock state induced by persistent MRSA bacteremia (which continued for approximately 20 days), secondary to respiratory infection: SPE.

In general, both pharmacokinetics and pharmacodynamics are important factors in determining the clinical efficacy of antibiotics. Among the various anti-MRSA drugs available, the pharmacodynamics of DAP against MRSA have been well assessed (8). Although cases of DAP-resistant MRSA have been reported worldwide (30-35), they remain still extremely rare in Japan. In general, DAP susceptibility testing is considered difficult and unreliable due to the need for precise concentrations of calcium in the culture medium, therefore most hospitals in Japan do not currently perform such testing. Interestingly, S. aureus isolates with elevated MICs of DAP can be selected by a prior exposure to VCM (36-38). Moreover, it was reported that the prior administration of VCM induces resistance to DAP (39). In this case, although VCM was administered for 5 days before DAP, the isolate was later proven to be sensitive to DAP (Table); that is, pharmacodynamically, DAP was confirmed to be effective against the pathogen. Some experts recommend higher dosages of DAP, namely at 8-10 mg/kg/dose once daily for the treatment of MRSA bacteremia (8), and therefore, the ineffectiveness of treatment in the present patient may be attributed to the low dose. Additionally, although rifampin has been shown to increase the bactericidal action of DAP against MRSA in some animal studies (40) and its clinical effectiveness in combination with DAP in treatment of SPE has been reported (22), we did not use this combination therapy because of our patient’s liver dysfunction. Thus, a higher dose of DAP combined with rifampin could yield a better outcome.

In the present case, the pharmacokinetic factors were considered to be the major reasons for the ineffectiveness of treatment. MRSA is originally a problematic pathogen from the aspect of pharmacokinetics since it frequently forms systemic disseminating lesions. Compared to VCM, DAP has a high penetration rate into various tissues and it can be used to treat a range of infections. However, as discussed above, respiratory infection is the exception; DAP-surfactant interactions in the alveolar tissue impair its antibacterial activity (41). SPE is an infection of the lung interstitial tissue, where surfactant cannot impair DAP activity; therefore SPE caused by MRSA is considered to be treatable with DAP (22). However, in SPE, a cavity is formed by necrosis due to an interruption of the blood flow caused by embolizing materials, and subsequently a secondary infection can occur in the necrotic lesions (38). As a result, intravenously administered antibiotics might not be delivered to the infectious foci. Moreover, it is possible that the septic inflammation of lung parenchyma can invade the intraalveolar space as the infection progresses, and in which case, DAP would be inactivated by surfactant.

Compared to DAP, LZD is not highly recommended for MRSA bacteremia at present (8). In the present case however, while DAP failed to achieve good results, LZD successfully controlled the persistent MRSA bacteremia. Although the precise reason for this was unclear, it can be explained by its high ability to penetrate into various tissues, including the lung. If LZD had been used as the initial therapy, then our patient’s condition might not have deteriorated.

To provide the best chance for patient survival, a proper diagnosis needs to be made as early as possible in order to administer appropriate treatment without delay. Endovascular infections are known to often cause persistent bacteremia (23). In the present case, the presence of IE was ruled out based on the negative findings of TTE/TEE and the autopsy. JVST was also suspected as a potential etiology of the treatment inefficacy. In fact, the etiology of SPE includes right-side IE, infectious thrombophlebitis, intravenous drug abuse, pelvic inflammatory disease, craniocervical suppurative disease, and prosthetic device infections (42-50); in the present case, repeated TTE/TEE, systemic CECT, and the autopsy could not reveal any apparent cause of SPE other than JVST of his internal jugular vein. Generally, JVST should be suspected as a source of infection when the bacteremia persists in patients with a past history of CVC placement. However, the occurrence of an intravascular thrombus formed by CVC insertion rarely causes problems, and in this case, a bacterial culture of the thrombus was negative and there were no inflammatory changes over mandibular angle or sternoleidomastoid muscle. According to these negative results, we considered that JVST was not likely. Rather, considering the clinical course, CLABSI was assumed to be responsible for SPE and subsequently the persistent MRSA bacteremia. SPE usually manifests with non-specific symptoms, and a definitive diagnosis is therefore difficult and often made later in the clinical course (51). It is important to be wary of a persistent high fever and a high-grade inflammatory state in patients with CVC. In the present case, a pancreas abscess extending to the posterior mediastinum, which was proven only at the time of autopsy, was considered to be the final cause of the patients’ death. However, the CT finding of his pancreas did not show any changes during the course and MRSA was not detected from the pancreas. As a result, it was unlikely that it had been the responsible focus of the recurrent bacteremia.

Infectious disease consultation is reported to be an independent predictor of fewer relapses and reduced mortality in patients with SAB (52-56). A delay in the administration of appropriate therapy for the treatment of MRSA bacteremia episodes is reported to lead to a worsening of the patient outcome (57). In the present case, early consultation and re-evaluation to select the most appropriate treatment in the early phase of the clinical course might have made it possi-
able to achieve a better outcome.

In summary, we herein presented the case of a patient with SPE and persistent bacteremia caused by MRSA that was uncontrollable with DAP, but successfully treated by LZD. MRSA-induced SPE has been considered to be treatable with DAP, but resistance to DAP may also occur as shown in this case. In patients with persistent MRSA bacteremia despite the availability of appropriate antibiotics, early and proper diagnosis of the infectious focus is essential to obtain a better prognosis.

The authors state that they have no Conflict of Interest (COI).

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