Lack of increase in time to blood culture positivity in a patient with persistent methicillin-resistant *Staphylococcus aureus* bacteremia predicts failure of antimicrobial therapy

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Time to positivity is an available parameter in automated blood culture systems. We report a patient with persistent methicillin-resistant *Staphylococcus aureus* bacteremia who received various regimens for treatment of methicillin-resistant *S. aureus*, and demonstrate that monitoring of the time to positive blood culture might be helpful in the early recognition of treatment failure.

Key words: Bacteremia; Methicillin resistance; *Staphylococcus aureus*

Introduction

Persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is associated with poor outcome [1-3]. Finding the source of persistent bacteremia and timely eradication of the focus are important [4]. However, the focus is sometimes not easily detected and surgical intervention might not be feasible. Although glycopeptides remain the standard first-line treatment [5], subsequent determination of when to start new anti-MRSA agents is difficult in patients with persistent bacteremia [6]. Time to positivity is an available parameter in automated blood culture systems, and is related to the source of infection and patient outcome in MRSA bacteremia [7]. We report a patient with persistent MRSA bacteremia in whom the parameter of time to positive blood culture was used during management with different anti-MRSA agents and surgical interventions.

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Case Report

A 74-year-old female had a history of coronary artery disease, hypertension, and diabetes mellitus with nephropathy. On December 29, 2006, she was admitted due to acute on chronic renal failure with presentation of dyspnea and decreased urine output. Hemodialysis was started after admission. Oral cephalexin (500 mg every 6 h) was prescribed for urinary tract infection. Cardiac catheterization on day 18 revealed severe three-vessel disease. A Permcath catheter was installed for hemodialysis on day 22. A 5 cm × 5 cm hematoma was found at the previous left femoral artery puncture site, and duplex ultrasound showed a pseudoaneurysm. An episode of fever was noted on day 32 and MRSA was isolated from blood samples (Fig. 1). Vancomycin (500 mg every 4 days) and cefmetazole (1 g every 3 days) were given starting on day 35. Cefmetazole was changed to piperacillin-tazobactam (3.375 g every 8 h) for persistent fever. Erythema with tenderness over the previous femoral pseudoaneurysm was found and repair of the left femoral artery was performed on day 43. Fever persisted and levofloxacin (500 mg every 2 days) was substituted for piperacillin-tazobactam. Aneurysm

excision with grafting and artery repair was performed on day 47 due to a right femoral artery pseudoaneurysm. Vancomycin was changed to teicoplanin (400 mg every 3 days) and rifampin (600 mg every day) because of persistent bacteremia despite adequate vancomycin trough level (16.2 μg/mL) on day 46. Right femoral wound debridement was performed again on day 63 due to tissue necrosis and poor healing. MRSA was isolated from the debrided tissue. Intermittent fever persisted, and the time to positivity did not change despite use of different glycopeptides alone and in combination regimens (Fig. 1). Minimal inhibitory concentration of vancomycin for the MRSA isolate (day 65) was 2 μg/mL by the Etest (AB Biodisk, Solna, Sweden). Transthoracic echocardiography revealed no evidence of infective endocarditis. The Permcath catheter was removed on day 68, and tip culture also yielded MRSA. Linezolid (600 mg every 12 h) was started on day 70, due to persistent bacteremia. Blood culture remained positive for MRSA after 5 days of linezolid use, but the time to positivity increased markedly, and finally became negative (Fig. 1). Defervescence was noted thereafter. After 42 days of linezolid use, the patient was transferred to a long-term care facility.

Discussion

The time to positive blood culture did not change in this case of invasive infection due to vancomycin-susceptible MRSA exhibiting an increased vancomycin minimal inhibitory concentration (2 μg/mL), despite repeated debridement and prolonged treatment with glycopeptide. Removal of the Permcath before linezolid use might have contributed to the resolution of persistent bacteremia. Linezolid is probably superior to vancomycin for the treatment of infection caused by MRSA isolates with increased vancomycin minimal inhibitory concentrations [8]. In addition to the removal of the catheter, better tissue penetration of linezolid might have accounted for resolution of our patient's persistent bacteremia [9].

Use of vancomycin as standard treatment for MRSA bactermia has been questioned, due to the numerous factors which can influence efficacy, including type of infection, existence of metastatic infections, performance of surgical intervention, and increased vancomycin minimal inhibitory concentrations of isolates [1-4,8-11]. Clinical signs and symptoms are used to determine glycopeptide treatment failure [8-11],
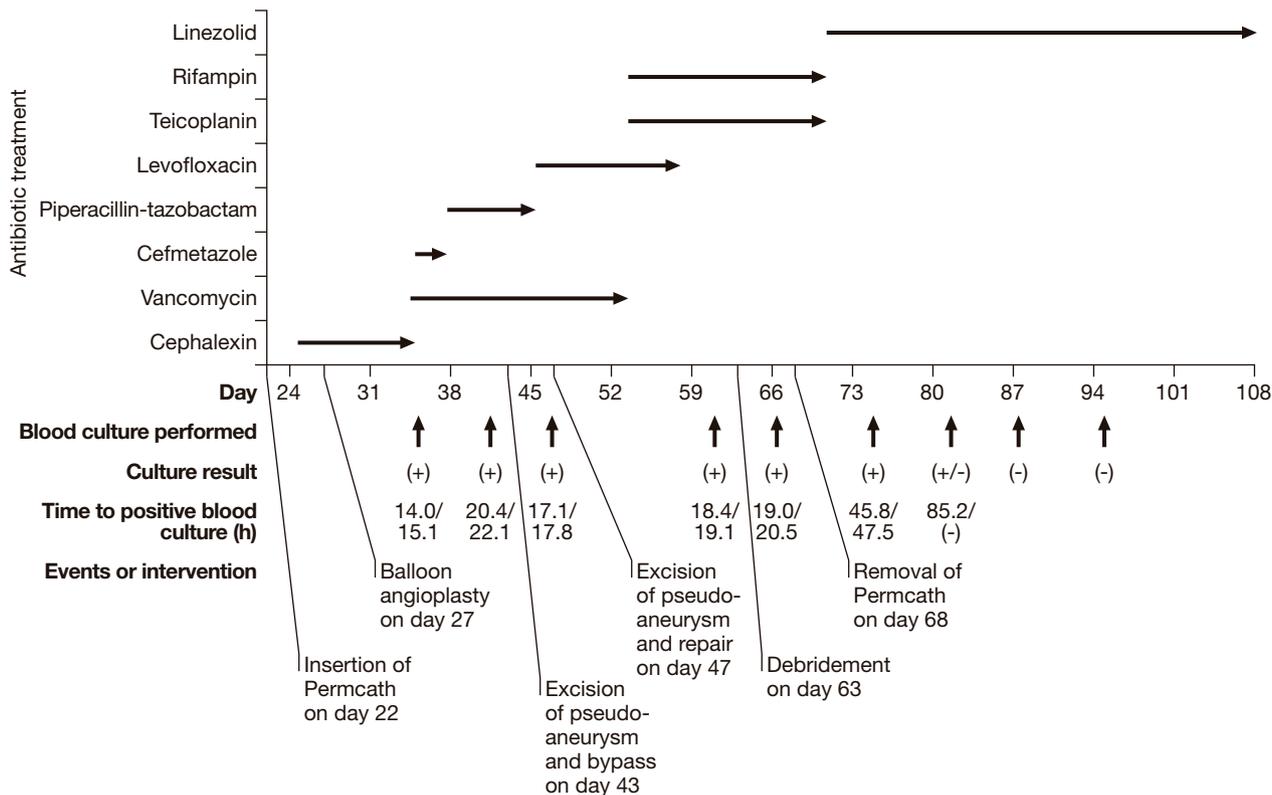

Fig. 1. Change in time to culture positivity in a patient with persistent methicillin-resistant *Staphylococcus aureus* bacteremia under different regimens of antimicrobial therapy and surgical intervention.

but this assessment approach may be subject to interference by concomitant infections; prolonged glycopeptide therapy for persistent bacteremia is not uncommon [8]. Persistent positive blood culture is the best measure of treatment efficacy, and we incorporated the parameter of time to positive blood culture to demonstrate the failure of glycopeptide treatment and success of linezolid.

In a previous study, growth of *S. aureus* in blood culture within 14 h after incubation suggested a high likelihood of endovascular infection sources, delayed clearance, and complications [7]. Our patient, in spite of a time to positive blood culture greater than 14 h, had an endovascular and soft tissue infection with persistent bacteremia. Catheter tip culture was also positive for MRSA, which might be another possible infection focus or a complication of previous bacteremia. For some patients with MRSA bacteremia, the infection focus might be cryptic, multiple, or not suitable for clinical monitoring of treatment efficacy. Regardless of the focus, lack of increase in time to positive blood culture might be used as an indicator of treatment failure.

Based on the findings of this case, we propose that time to culture positivity may predict the success of antimicrobial therapy. However, there are many confounding factors (such as inoculum size and removal of the central catheter) involved in determining time to culture positivity. Thus, a prospective study should be conducted to test this hypothesis.

In summary, monitoring the time to positive blood culture might be helpful in early recognition of treatment failure in patients with persistent MRSA bacteremia. Modification of management, whether surgical intervention or change of antimicrobial agent, should be considered if the time fails to increase during antimicrobial therapy.

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