EDITORIAL

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Persistent methicillin-resistant *Staphylococcus aureus* bacteremia: do we need a new therapeutic strategy?

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Although vancomycin continues to be a mainstay in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA), significant shortcomings of this therapy have been demonstrated [1]. Vancomycin has several pharmacokinetic and pharmacodynamic limitations, namely slow bactericidal activity, poor tissue penetration, reduced activity against biofilm pathogens, and an increasing minimum inhibitory concentration (MIC) for select vancomycin-susceptible *S. aureus* strains [1]. Furthermore, persistent MRSA bacteremia has been increasingly recognized among hospitalized patients and raises concerns because it develops despite the administration of appropriate antibiotics such as vancomycin or teicoplanin [2,3].

Several studies were recently published in Korea regarding the clinical features and predictors of persistent *S. aureus* bacteremia [3-5]. Yoon et al. [3] reported that predictors of persistent MRSA bacteremia in patients treated with vancomycin include retention of implicated medical devices, MRSA infection of at least two sites, and a vancomycin MIC of 2 mg/L. In addition, Chong et al. [4] reported that many patients (15.7%) with *S. aureus* bacteremia, particularly those with community-onset bacteremia, bone and joint infection, central venous catheter-related infection, metastatic infection, MRSA isolates, and late source control, have persistent bacteremia despite 7 days of antibiotic treatment. In a study including persistent bacteremia with eradicated foci, *agr* dysfunction in *S. aureus* was significantly associated with persistent bacteremia [5]. Reduced susceptibility to glycopeptides in MRSA clinical isolates is considered to be a risk factor for failure of glycopeptide therapy, and bacteremic patients with a poor response to glycopeptide therapy had 2.8- and 4.8-fold higher rates of MRSA isolates displaying elevated teicoplanin and vancomycin MICs, respectively, than patients with single isolates ($p < 0.001$) [6].

In the current issue of *The Korean Journal of Internal Medicine*, Ok et al. [7] also assessed the clinical features of and predictors for persistent MRSA bacteremia with glycopeptide treatment. Of 79 patients with MRSA bacteremia, 31 (39.2%) had persistent MRSA bacteremia, which is a relatively higher proportion than previous studies. Metastatic infection at presentation and delayed catheter removal in catheter-related infection were

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independent predictors for persistent MRSA bacteremia, which are similar findings to those of previous studies [2-4]. Notably, persistent MRSA bacteremia was found more frequently in patients with a time to blood culture positivity of < 11.8 hours, highlighting the clinical significance of time to positivity in persistent MRSA bacteremia [7]. The persistent MRSA bacteremia group had a 58.1% mortality rate, which was relatively higher than those in previous studies [3,7]. Persistent bacteremia causes high rates of morbidity and attributable mortality; thus, early aggressive treatment strategies, such as early source control and higher vancomycin trough levels, should be implemented in patients with risk factors for persistent bacteremia [4]. However, no consensus has emerged with regard to appropriate antimicrobial therapy for persistent MRSA bacteremia despite the fact that failure is common and frequently leads to death [2].

What is a feasible new therapeutic strategy for the management of persistent MRSA bacteremia? First, rifampicin or gentamicin is frequently combined with a glycopeptide to achieve bactericidal synergy in patients with persistent MRSA infection [1]. However, treatment with a rifampicin-containing regimen for MRSA bacteremia is likely to rapidly induce rifampicin resistance, especially in elderly patients [8]. The higher mortality rate of patients with emergence of rifampicin-resistant MRSA during rifampicin-containing treatment and the higher frequency of hepatotoxicity with current rifampicin use among patients with MRSA bacteremia warrant clinical attention and further study [8]. Furthermore, the development of rifampicin resistance during treatment with a rifampicin-containing regimen in a patient with MRSA infective endocarditis has been reported [9]. The occurrence of nephrotoxicity and ototoxicity caused by aminoglycosides in predisposed patients limits the use of aminoglycosides in this population. Second, teicoplanin has shown promise as an alternative agent for the treatment of MRSA infections. However, a previous study in Taiwan showed that persistent MRSA bacteremia in hospitalized elderly patients was associated with high rates of mortality, and no significant difference in the survival rate was found between patients who received vancomycin and those who received teicoplanin treatment [10]. Finally, linezolid and daptomycin can be useful alternatives to vancomycin or teicoplanin for treating persistent MRSA bacteremia. A previous study showed that the early microbiological response (i.e., negative follow-up blood culture results within 72 hours) was significantly higher in the linezolid-based salvage therapy group than in the comparison group (75% vs. 17%; $p = 0.006$) [2]. The addition of an aminoglycoside or rifampicin to vancomycin was not successful in treating any of the patients, whereas linezolid-based therapy gave an 88% salvage success rate ($p < 0.001$) [2]. The S. aureus-related mortality rate was lower for patients treated with a linezolid salvage regimen than for patients continually treated with a vancomycin-based regimen (13% vs. 53%; $p = 0.030$) [2]. In another study performed in a Korean hospital, linezolid-based salvage therapy revealed a tendency toward better outcomes than the comparator despite its worse prognostic factors compared with those of the glycopeptide-based therapy group, suggesting that linezolid-based salvage therapy should be considered in patients with persistent MRSA bacteremia despite the use of glycopeptide therapy [10]. Although the efficacy of linezolid-based regimens is likely to be good, cytopenia and neurotoxicity may limit their prolonged use for the 4 weeks that are needed to treat complicated *S. aureus* bacteremia [2]. Unfortunately, daptomycin is not yet available in Korea, although it can be efficacious for the treatment of *S. aureus* bacteremia.

The findings reported by Ok et al. [7] challenge us to revisit a fundamental therapeutic approach against persistent MRSA bacteremia. Clinicians in Korea and elsewhere may be able to use these data to consider alternative options for the treatment of persistent MRSA bacteremia, but this will not be easy. The current crisis in antibiotic development and the public health threat posed by antimicrobial resistance impose a reappraisal of therapeutic strategies that have been successful in the past. Given the poor outcome of persistent MRSA bacteremia and the lack of therapeutic efficacy of vancomycin, further studies are needed to define the optimal antimicrobial therapy for persistent MRSA bacteremia. Indeed, we look forward to further clinical advancement of therapeutic strategies and to development of new, potent anti-MRSA antimicrobials.

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Conflict of interest

No potential conflict of interest relevant to this article is reported.

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