Cost-Effectiveness Analysis of Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia and Endocarditis Is a Difficult Issue

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(See the article by Bhavnani et al on pages 691–8)

Methicillin-resistant Staphylococcus aureus (MRSA) was first detected in 1961. Today, MRSA is widely spread around the world. In the United States [1] and in many European countries, 25%–50% of S. aureus isolates are MRSA [2], even if some countries (eg, the Netherlands and the Scandinavian countries) have a low level of cases of invasive MRSA infection.

Invasive MRSA infections, such as bacteremia and endocarditis, are difficult to treat because the treatment options are limited. MRSA bacteremia also has a higher mortality rate than does bacteremia due to methicillin-susceptible S. aureus (MSSA) [3]. Infective endocarditis due to MRSA has a trend toward a higher mortality rate compared with that due to MSSA [4]. Many of the patients are immunocompromised with underlying diseases and may have intracardiac devices or intravenous catheters in place, and such infections are difficult to treat without replacement of these devices.

Vancomycin, a glycopeptide, is the first-line drug for treatment of invasive MRSA infection. However the failure rate is high, the bactericidal activity is poorer than that of the β-lactams, and nephrotoxicity is a problem. Failure of vancomycin can be attributed to low tissue penetration [5] and increasing minimum inhibitory concentrations (MICs) [6] associated with increased cell wall thickness [7], which is the barrier for penetration of the antibiotic. Cases of bacteremia due to MRSA with a high MIC of vancomycin have been shown to have a higher mortality rate than the rate for MRSA with a low MIC of vancomycin [8]. In such cases, higher doses of vancomycin have been suggested, but higher doses may also cause more nephrotoxic adverse effects [9].

Daptomycin, a bactericidal cyclic lipopeptide produced by Streptomyces roseosporus, has activity against several gram-positive bacteria, including MRSA. It was discovered in the 1980s but was withdrawn because of adverse effects, such as myositis when high doses were used; development of the drug was aborted. Daptomycin was reintroduced in the 1990s, and lower doses were used. It was approved for use in the United States and the European Union for complicated soft-tissue and skin infections in 2003.

A randomized study that compared conventional treatment with daptomycin treatment for bacteremia and native valve infective endocarditis due to S. aureus (MSSA and MRSA) was performed and published in 2006 and demonstrated non-inferiority for daptomycin for bacteremia and right-side endocarditis [10]. That study was also the main reason why daptomycin was registered for these indications in the United States and the European Union.

In this issue of Clinical Infectious Diseases, Bhavnani et al [11] compare the cost-effectiveness of daptomycin with that of vancomycin-gentamicin in patients with MRSA bacteremia and endocarditis. Cost-effectiveness studies of daptomycin and vancomycin have been presented for complicated skin and soft-tissue MRSA infections [12]. However, until now, no cost-effectiveness studies have been published on the treatment of MRSA bacteremia and endocarditis. Bhavnani et al [11] used data from 89 patients with MRSA bacteremia and endocarditis described in a study by Fowler et al [10] and performed a subset analysis. The study included patients with left-side native valve endocarditis, right-side complicated endocarditis, complicated bacteremia, and uncomplicated bacteremia due to MRSA. The daily doses were 6 mg/kg intravenously for daptomycin and 1 g intravenously twice per
day for vancomycin, with dose adjustment for vancomycin based on renal function.

Cost-effectiveness ratio was defined as the costs divided by the proportion of successes. Three cost-strata were used. In stratum 1, the costs of drug acquisition was compared between the arms; the findings were more favorable for vancomycin-gentamicin than for daptomycin. Stratum 2 included the costs from stratum 1 plus the costs of therapy for treatment failures and adverse events and the costs of therapeutic drug monitoring; the findings were more favorable for vancomycin-gentamicin. Finally, stratum 3 included all of the information from stratum 2 plus bed costs. In stratum 3, the cost-effectiveness for the treatments was similar.

Rehm et al [13] evaluated 88 cases of MRSA infection reported in the same study by Fowler et al [10], providing additional information. The patients in the vancomycin-gentamicin arm, for example, more often had foreign intravascular materials present, compared with patients in the daptomycin arm.

Treatment success rates were similar in both arms for cases of infective endocarditis, 0% of cases of left-side endocarditis, and 50% of cases of right-side complicated endocarditis [13]; these are low values. In cases of bacteraemia, daptomycin had a more favorable treatment success rate (for uncomplicated cases, 60% for daptomycin and 45% for vancomycin-gentamicin; for complicated cases, 45% for daptomycin and 27% for vancomycin-gentamicin). Patients in the daptomycin arm more often stayed in the intensive care unit, and the mortality rate in the daptomycin arm was higher than that in the vancomycin-gentamicin arm (27% vs 19%), although the difference was not statistically significant [11, 13]. There were also more relapses of MRSA septicemia in the daptomycin arm than in the vancomycin-gentamicin arm (27% vs 21%). Patients with persistent MRSA bacteraemia had a high mortality rate in both treatment arms (~60%) [13].

In the article by Bhavnani et al [11], 1 patient was treated with nafcillin initially as a result of misleading information about the microbiological agent; in the article by Rehm et al [13], that patient was excluded. Perhaps Bhavnani and colleagues should have done the same. In addition, cases of left-side endocarditis due to MRSA were included in the analysis; the US Food and Drug Administration and the European Medicines Agency have not approved use of daptomycin for this indication.

Therapeutic failures in the daptomycin arm were treated with vancomycin and/or rifampin, and failures in the vancomycin-gentamicin arm were treated with vancomycin and/or rifampin and/or linezolid. Linezolid is very expensive and could explain the cost differences between the groups. Therapeutic drug monitoring was also more frequently used in the vancomycin-gentamicin arm.

It is not surprising that renal impairment was found more frequently in the vancomycin-gentamicin arm. The role for gentamicin as an adjuvant treatment for S. aureus bacteremia and endocarditis was recently discussed and reconsidered, because nephrotoxicity occurs even with short-course regimens [14]. For patients with impaired renal function, daptomycin could be a treatment option.

There are several case reports about daptomycin treatment failures for MRSA bacteremia [15–17] and endocarditis [18]. There are also reports of development of daptomycin resistance after vancomycin treatment [19].

In the study by Bhavnani et al [11], the dosage of daptomycin was 6 mg/kg per day. In 1 case report, a higher dosage of daptomycin (12 mg/kg per day) was required for treatment of infective endocarditis [20]. There are additional ongoing studies of treatment of MRSA endocarditis and bacteremia with daptomycin or vancomycin; in one study (http://clinicaltrials.gov/ct2/show/NCT00695903), the dosage of daptomycin (10 mg/kg per day) is higher than that in the study by Bhavnani and colleagues. If a higher dose of daptomycin is used, it would contribute to less cost-effectiveness in the daptomycin arm. A pharmacokinetic study is being performed as well (http://clinicaltrials.gov/ct2/show/NCT00695903); in that study, patients with pacemakers were required to remove them before they entered the study.

Therapeutic drug monitoring for daptomycin has been described in pediatric patients [21]. Therapeutic drug monitoring would probably be used more frequently if higher doses of daptomycin were used and could be considered in the cost-effectiveness analysis.

Vancomycin is not optimal for treatment of MRSA infection. Elevated MICs of vancomycin have been reported. Glycopeptide-intermediate S. aureus was described in Japan in 1996. Clinical cases of MRSA infection with high-level resistance to vancomycin were reported in the United States in 2002. Subpopulations of heterogeneous vancomycin-intermediate S. aureus strains have been found in patients with bacteremia [22] and endocarditis [23]. In one study, heterogeneous vancomycin-intermediate S. aureus strains were successfully treated with daptomycin in vitro [24].

The study by Bhavnani et al [11] included a small sample of patients with bacteremia and endocarditis caused by MRSA. These infections are complicated and life-threatening and require close monitoring and treatment.

The cost-effectiveness analysis seems difficult to evaluate in a study in which <50% of patients were cured while receiving any of the study drugs and in which the mortality was high. Sixty-six (74%) of the 89 cases in this study were complicated; there were no cases of uncomplicated right-side MRSA endocarditis. Some of the patients who died had pacemakers in place that were removed; this could have contributed to the high mortality rate.

There is certainly an important role for daptomycin treatment in patients with endocarditis and bacteremia due to MRSA,
but additional studies are needed. For uncomplicated cases of right-side endocarditis due to MRSA, daptomycin could be an alternative treatment. A cost-effectiveness analysis involving such patients would be interesting, but no such patients were in the present study.

Performance of cost-effectiveness analysis in a study of a heterogeneous patient population with complicated MRSA bacteremia and endocarditis is a difficult task. Each case requires individualized treatment, to improve the prognosis and survival for these severely ill patients.

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References