Introduction

The incidence of infections caused by multidrug-resistant \textit{Staphylococcus aureus} and enterococci is increasing. In a recent study of European intensive care units (ICUs), 30% of all infections were attributable to \textit{S. aureus} and 60% of these were oxacillin resistant or methicillin resistant.\textsuperscript{1} In the USA, in 1996 alone, \textit{S. aureus} infections in the New York area claimed 1400 lives and cost New York City $US 435 million; 29% of these infections were resistant to all antibiotics except vancomycin, and accounted for 48% of the mortality.\textsuperscript{2} Nosocomial outbreaks of vancomycin-resistant enterococcal infection have occurred in the UK, Europe and the USA.\textsuperscript{3-5} Infections caused by these resistant pathogens are clinically important and are associated with additional economic costs as compared with those due to susceptible organisms. This review will present data on the cost implications of infection with methicillin-resistant \textit{S. aureus} (MRSA) and vancomycin-resistant \textit{Enterococcus faecium} (VREF). It will also provide strategies for controlling costs, while maximizing the effectiveness of the few remaining antimicrobials available for the treatment of these increasingly prevalent nosocomial infections.

General concepts

Demonstrating the true impact and determining the real cost of treating resistant infections is difficult because of the compounding factors of patient characteristics and the problem of determining cause and effect. Several patient characteristics are associated with the development of infection with resistant strains of bacteria. For example, risk factors for the development of nosocomial MRSA infections include previous antibiotic use, increased age, severity of underlying illness and duration of hospitalization.\textsuperscript{6} Similarly, the risk factors for developing post-operative infections caused by MRSA include previous antimicrobial therapy, prolonged hospitalization, severe underlying disease, old age and multiple invasive procedures.\textsuperscript{7} Furthermore, cause and effect must be clarified when assessing duration of hospitalization and mortality rates associated with infection due to resistant pathogens. Patients infected with MRSA have a longer length of stay and a higher rate of mortality than patients infected with methicillin-susceptible strains of \textit{S. aureus} (MSSA).\textsuperscript{6,8} Similarly, in a study of patients with VREF infection as compared with vancomycin-susceptible \textit{E. faecium} (VSEF) infection, multivariate analyses showed that the duration of

Costs of treating infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci

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Ifection with methicillin-resistant \textit{Staphylococcus aureus} (MRSA) or vancomycin-resistant \textit{Enterococcus faecium} (VREF) increases the risk of mortality and results in prolonged hospitalization and high utilization of costly treatment modalities. Measures to prevent the spread of MRSA (and possibly VREF) include patient isolation and decontamination, hygiene measures, ward closure, and screening of patients and staff for carriage. In seriously ill patients, the increased use of vancomycin for the treatment of MRSA can lead to the emergence of VREF colonization/infection. Quinupristin/dalfopristin is effective in the treatment of MRSA infections, including nosocomial pneumonia, skin and soft tissue infection, and septicemia. In the treatment of nosocomial pneumonia, clinical success rates were equivalent between quinupristin/dalfopristin and vancomycin. In the context of a hospital policy which emphasizes effective hygiene measures and the prudent use of antibacterials, quinupristin/dalfopristin is an effective antimicrobial that can help to control the high costs associated with multiresistant MRSA and VREF infections.

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hospitalization was independently associated with VREF infection. However, as stated above, duration of hospitalization and severity of underlying illness are also risk factors for the development of nosocomial MRSA. Thus, in a pharmaco-economic study, the experimental model must be able to clarify cause and effect. Specifically, it must differentiate whether an increased duration of hospitalization and rate of mortality represent: (i) an increased predisposition to infection with a resistant pathogen during prolonged hospitalization and/or severe illness; or (ii) result of infection with a resistant pathogen. This can usually be ensured by providing a control group matched for age, underlying conditions and severity of illness.

Methicillin-resistant S. aureus

As noted above, the association between infection with MRSA and a prolonged length and increased cost of hospitalization has been documented. Nosocomial outbreaks of MRSA infection between 1971 and 1980 were investigated by the CDC in the USA. In the two outbreaks in which patients infected with MRSA were matched with controls who had positive cultures for non-epidemic, methicillin- and gentamicin-susceptible S. aureus, the average length of stay associated with MRSA infection was approximately twice as long as that associated with MSSA infection (57 versus 24 days and 27 versus 16 days). A review of the literature found more adverse health and economic effects associated with resistant than with susceptible S. aureus infections. Another study also showed that patients with MRSA infection had an increased duration of hospitalization as compared with patients with MSSA infection. MRSA infection was associated with a 250% increase in hospital costs, from US$ 24,280 for MSSA to US$ 64,370 for MRSA.

In their epidemiological observations during a community-acquired outbreak of MRSA, Saravolatz et al. matched patients by age, gender, history of parenteral drug abuse, infection site, race and underlying illness. Among iv drug abusers infected with MSSA (n = 24) as compared with MRSA (n = 24), the length of hospitalization was 20 days and 30 days, respectively. Previous antibiotic use was documented in half of the MSSA group but in all but one of the MRSA group. The only deaths (2/24) occurred in drug abusers with MRSA infections. Similar results were found among the patients who were not iv drug abusers. In the MRSA group, length of hospitalization (13 days) was more than double that of the MSSA group (6 days). Previous antibiotic use was documented in 44% (7/16) of MSSA-infected patients and 63% (10/16) of MRSA-infected patients; previous hospitalization within 4 months was documented in 19% (3/16) and 75% (12/16), respectively.

The prevalence of MRSA has increased to such an extent that outbreaks are commonly encountered in critical care areas. The cost of an ICU patient can be divided into a fixed component and a variable component dependent on the patient’s treatment. Blunt et al.2 equated the variable component with the therapeutic intervention scoring system (TISS), to ascertain the impact of MRSA colonization or infection on outcome and degree of intervention among 35 patients with cultures positive for MRSA either before or during their admission to a general ICU. The MRSA-positive group and a matched control group (n = 35) were similar for age, gender, APACHE II score, risk of death and admission diagnosis (Table I). There were no statistically significant differences between the MRSA-positive and control groups in mortality in the ICU (seven deaths in each group), but a non-significant trend towards increased mortality in the MRSA-positive group in the hospital ward (seven and three deaths, respectively). There was no statistically significant difference between the two groups in the mean daily TISS. However, breakdown of the TISS data revealed that MRSA patients received significantly more days of treatment with inotropes (P < 0.05), antibiotics (P < 0.01), multiple antibiotics (P < 0.01),

<p>| Table I. Baseline characteristics and outcomes (mean ± s.e.m., unless otherwise indicated) in patients with MRSA infection, and matched controls, in the intensive care unit |
|-------------------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>MRSA (n = 35)</th>
<th>Control (n = 35)</th>
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</thead>
<tbody>
<tr>
<td>age</td>
<td>54.8 (± 2.6)</td>
<td>59.7 (± 2.8)</td>
</tr>
<tr>
<td>gender (male:female)</td>
<td>18:17</td>
<td>21:14</td>
</tr>
<tr>
<td>APACHE II</td>
<td>22.3 (± 1.7)</td>
<td>22.5 (± 1.7)</td>
</tr>
<tr>
<td>APACHE II derived risk of death</td>
<td>40.4 (± 4.9)</td>
<td>42.2 (± 4.9)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean daily therapeutic intervention score (TISS)</td>
<td>25.1 (± 1.4)</td>
<td>27.1 (± 1.1)</td>
</tr>
<tr>
<td>median length of stay (days)</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>died in ICU (number)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>died on ward (number)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>discharged (number)</td>
<td>21</td>
<td>25</td>
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Patients were treated with either developed a computerized decision the number of deaths per 100 person-days of examined risk factors and mortality conducted a controlled study The USA study included Puerto Rico, 12,13

| Patients with methicillin-resistant and oxacillin 2 g 6 hourly (USA study) precautions about drug sensitivity and tolerance, this study showed that the costs of VREF infection are high, as documented by expected cost per hospitalization (ampicillin, US$ 43,831; vancomycin, US$ 43,637; VREF, US$ 45,465),

**Vancomycin-resistant E. faecium**

The cost implications of VREF have been studied as extensively as those of MRSA, and the negative impacts are even clearer. Landry, Kaiser & Wenzel conducted a controlled study of 97 patients with nosocomial enterococcal bacteraemia. Ninety-seven controls were case-matched for age, gender, primary diagnosis and surgical procedures when applicable. Among the patients with enterococcal bloodstream infection as compared with case controls, mortality was increased more than four-fold (to 53% from 12%) and the median hospital stay was increased more than three-fold (to 60 days from 19 days).

Tornieporth et al. examined risk factors and mortality associated with VREF infection or colonization at a tertiary care hospital, by comparing 145 patients with VREF isolates (cases) with 145 patients with VSEF isolates (controls). The number of deaths per 100 person-days of hospitalization after diagnosis did not differ significantly between VREF patients (1.2) and controls (0.8). However, multivariate analyses found that the duration of hospitalization (≥7 days), intrahospital transfer between floors, use of antimicrobials (i.e. vancomycin and third-generation cephalosporins) and duration of vancomycin use (≥7 days) was independently associated with VREF infection or colonization.

Goss et al. developed a computerized decision analytical model to estimate the impact of nosocomial E. faecium bacteraemia on patient survival, length of stay and treatment costs. Patients were treated with either ampicillin; vancomycin, if the patient was allergic to ampicillin or the organism was ampicillin resistant; or no additional therapy (VREF) if the patient was allergic to ampicillin and the E. faecium was also resistant to both ampicillin and vancomycin. Under baseline model assumptions about drug sensitivity and tolerance, this study showed that the costs of VREF infection are high, as documented by expected cost per hospitalization (ampicillin, US$ 43,831; vancomycin, US$ 43,637; VREF, US$ 45,465),

<table>
<thead>
<tr>
<th>Treatment duration in two randomized, open-label, multicentre studies of complicated Gram-positive skin and skin structure infection (clinically evaluable population)</th>
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<tr>
<td><strong>Quinupristin/dalfopristin</strong></td>
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<tr>
<td><strong>Worldwide study</strong></td>
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<td>13</td>
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<td>14</td>
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*Vancomycin for methicillin-resistant pathogens and cefazolin (worldwide study) or oxacillin (USA study) for methicillin-susceptible pathogens.*
length of stay (ampicillin, 56.9 days; vancomycin, 57.0 days; VREF, 60.6 days) and percentage discharged alive (ampicillin and vancomycin, 64.2%; VREF, 44.2%).

In an animal model of endocarditis, exposure of the VanB phenotype of \textit{E. faecalis} to vancomycin resulted in the selection of bacteria that were highly resistant to teicoplanin. The authors concluded that the efficacy of teicoplanin was significantly reduced after pre-treatment with vancomycin and recommended that teicoplanin should be administered first if there is suspicion of acquired VanB resistance. Glycopeptide usage policy should, therefore, take this into account when there is a high prevalence of VanB resistance.

**Discussion**

Infection with MRSA or VREF increases the risk of mortality, and results in prolonged hospitalization and high utilization of costly treatment modalities. Thus, preventive and control measures should be vigorously pursued.

Measures to prevent the spread of MRSA include patient isolation and decontamination, hygiene measures, ward closure, and screening of patients and staff for carriage. In contrast to MRSA, the effectiveness of isolation and other control measures in preventing the nosocomial spread of VREF remains to be evaluated. Strict adherence to barrier isolation measures or implementation of the use of gowns and gloves has been successful. However, the control of hospital outbreaks may be complicated by the existence of a large pool of untreated carriers.

The treatment options for established infection with these multidrug-resistant strains are limited. MRSA are frequently resistant to other antimicrobials, including the aminoglycosides, macrolides, lincosamides, tetracyclines, cephalosporins, carbapenems, β-lactamase inhibitor combinations and sulphonamides. Antibiotics with potential or proven activity against MRSA include the fluoroquinolones, fusidic acid, rifampicin, vancomycin and the new streptogramin combination, quinupristin/dalfopristin. Careful interpretation of \textit{in vitro} susceptibility tests is necessary to choose the optimal therapy. Erythromycin-susceptible and -resistant strains of MRSA have been demonstrated to be highly susceptible \textit{in vivo} to quinupristin/dalfopristin. \textit{In vivo}, decreased susceptibility to quinupristin/dalfopristin was noted in macrolide-resistant MRSA which were constitutively resistant to erythromycin.

During the last 15 years, emerging high level resistance of enterococci to aminoglycosides and resistance to ampicillin, have resulted in increased reliance on vancomycin therapy. The emergence of glycopeptide resistance in \textit{E. faecium}, which may lead to resistance to both vancomycin and teicoplanin (VanA phenotype) or to vancomycin only (VanB phenotype) has left few treatment options other than quinupristin/dalfopristin; anecdotal reports indicate that chloramphenicol, rifampicin, bacitracin, doxycycline and novobiocin, as well as combination therapy with ampicillin/sulbactam and gentamicin or penicillin, can be successful against enterococci, but the development of resistance during treatment and clinical failure are both common events. However, it should be noted that inducible macrolide-resistant strains of VREF are of decreased susceptibility \textit{in vivo} to quinupristin/dalfopristin.

Improving outcomes and minimizing costs are central to the institutional management of MRSA and VREF infections. However, a primary long-term goal must be to maintain the effectiveness of the few remaining antimicrobials that are currently available for the treatment of these increasingly prevalent nosocomial infections, via establishment of rational prescribing policies. As resistance is less likely to spread in a hospital unit if antimicrobial use is varied, two strategies proposed by Schentag are: to rotate the antimicrobial agent used between patients (especially if resistance begins to follow the use of a particular agent); and to alternate between classes of antimicrobials. However, the long-term consequences of these strategies have never been established. Importantly, formulations that attempt to curtail costs by limiting antimicrobial choices may actually have the opposite effect by contributing to the emergence of resistance.

At present, the only treatment option for many strains of VREF is quinupristin/dalfopristin. In contrast, both the glycopeptides (vancomycin or teicoplanin) and quinupristin/dalfopristin are effective for the treatment of MRSA infection. Among seriously ill patients; however, the increased use of vancomycin can lead to the emergence of VREF colonization/infection, as discussed above. Data from Edmond have shown that these seriously ill patients are colonized by both VREF and methicillin-resistant staphylococci (MRSA and methicillin-resistant \textit{Staphylococcus epidermidis} (MRSE)). At present, the only treatment that has been shown to eradicate effectively both methicillin-resistant staphylococci and VREF is quinupristin/dalfopristin.

The recent emergence of \textit{S. aureus} with reduced susceptibility to vancomycin (vancomycin-intermediate \textit{S. aureus} (VISA) strains) in Japan, the USA and France emphasizes the importance and urgency of such a rational prescribing policy for the treatment of MRSA infections. The VISA strains in the USA remained susceptible to chloramphenicol, rifampicin, co-trimoxazole and tetracycline (the Michigan case) and to gentamicin, co-trimoxazole, tetracycline and imipenem (the New Jersey case). Both patients continued to receive therapy on an outpatient basis and, in the latter case, VISA was no longer isolated at the next admission. All VISA strains tested to date have been sensitive to quinupristin/dalfopristin.

A rational prescribing policy would also help to preserve the efficacy of the glycopeptides for other uses, such as oral therapy for the treatment of \textit{Clostridium difficile} colitis.
In conclusion, infections due to MRSA and VREF are of increasing concern in some geographical areas. They are associated with increased mortality, morbidity and health costs. The therapeutic options are, in some instances, limited to a small number of compounds. Quinupristin/dalfopristin appears to be one of the most attractive options. Prevention of infection, through development of standards for the optimal use of antibiotics in hospital and extensive application of hospital hygiene measures, appears to be the only way to control further spread of multidrug-resistant bacterial strains.

References


