New strategies to identify patients harbouring antibiotic-resistant bacteria at hospital admission

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ABSTRACT

Nosocomial infections caused by antibiotic-resistant bacteria are associated with high morbidity and mortality worldwide. Most prevention strategies focus on cross-transmission, but the endemic state inside the hospital is also maintained through the influx of patients colonised or infected with antibiotic-resistant bacteria, balanced by the efflux of colonised patients following discharge. Epidemiological research has demonstrated that eradication can be achieved by preventing the influx of resistant bacteria. The presence of a central venous catheter and a history of methicillin-resistant Staphylococcus aureus (MRSA) infection or colonisation are associated significantly with methicillin-resistant staphylococcal bacteraemia at admission. Previous antibiotic therapy and transfer from long-term care facilities or nursing homes are associated with bacteraemia caused by methicillin-resistant coagulase-negative staphylococci, while skin ulcer and cellulitis are independent risk-factors for MRSA bacteraemia. A scoring system using point values has been developed and validated to identify patients positive for vancomycin-resistant enterococci at admission. Six variables were identified: age > 60 years (2 points); hospitalisation in the previous year (3); use of two or more antibiotics during the previous 30 days (3); transfer from another hospital or long-term care facility (3); a requirement for chronic haemodialysis (2); and a previous history of MRSA infection (4). With a point score cut-off of ≥ 10, the specificity of this prediction rule is 98%. Knowledge of variables identifying patients at high risk for being colonised or infected with antibiotic-resistant bacteria may assist clinicians in targeting preventive measures and streamlining the use of vancomycin. Current studies are analysing risk-factors for harbouring multiresistant Gram-negative bacteria at hospital admission.

Keywords Antibiotic resistance, healthcare-associated infections, nosocomial infections, prevention, review, risk-factors

Accepted: 17 September 2005


INTRODUCTION

Nosocomial infections pose a significant threat to patients worldwide, with a recent report of 4% excess mortality for infections associated with medical care, and 23% mortality for post-operative septicemia [1]. Most deaths associated with nosocomial infections are caused by antibiotic-resistant bacteria. European surveillance has documented that methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant Gram-negative bacteria are increasing rapidly in importance [2]. In the USA, National Nosocomial Infection Surveillance data demonstrated that the frequencies of MRSA, methicillin-resistant coagulase-negative staphylococci (MR-CoNS) and VRE in intensive care units in 2002 were 57%, 89% and 27%, respectively [3].

An endemic state of nosocomial infections resistant to antibiotics may be achieved by a constant influx of microorganisms (e.g., MRSA and VRE) into the healthcare setting from newly admitted patients who are colonised or infected with antibiotic-resistant bacteria, followed by cross-transmission among hospitalised patients, with de-novo acquisition and efflux of antibiotic-
resistant bacteria from the hospital into the community following the discharge of patients. In order to develop effective prevention strategies, it is first necessary to understand the various components responsible for this endemic state. Until now, most prevention strategies have focused on the middle component, i.e., the production of guidelines for antibiotic therapy and prevention of cross-transmission among hospitalised patients, and between hospital staff and patients. However, the influx of antibiotic-resistant bacteria into the healthcare setting may be a more important factor in the establishment of endemicity. In a cohort of patients with MRSA and vancomycin-resistant enterococcal bacteraemia, stratified by day of hospitalisation, an unexpectedly high number of cases were diagnosed within 48 h of hospitalisation [4]. A mathematical model describing the transmission dynamics of VRE demonstrated that eradication could be achieved by prevention of this influx [5]. The model demonstrated that, although 100% compliance with hand washing or a 1:1 nurse to patient ratio would decrease the overall prevalence of VRE in the unit substantially, the only intervention that achieved complete eradication of VRE from this patient population over time was the prevention of influx of VRE into the unit.

On the basis of these findings, it seems necessary to define the epidemiological characteristics of patients at higher risk for being infected or colonised with antibiotic-resistant bacteria at hospital admission. This would allow targeted screening procedures and commencement of the most appropriate empirical antibiotic therapy in order to reduce the spread of antibiotic-resistant infections and related mortality.

METHICILLIN-RESISTANT COAGULASE-NEGATIVE STAPHYLOCOCCI

Several studies, including the SENTRY programme, which provides surveillance data from the USA, Canada, Latin America and Europe [3,6], have shown that CoNS are the third most common pathogens recovered from positive blood cultures of community or hospital origin, with attributable mortality rates of up to 14%.

In order to elucidate the epidemiology of bacteraemia caused by CoNS that was diagnosed at hospital admission, two case-control studies were performed [7]. The case–case-control study design, which compares risk-factors among two groups of cases and a control group of patients who do not have the disease, was chosen to address specifically the impact of previous antibiotic therapy on the risk of bacteraemia caused by antibiotic-resistant pathogens. It has been shown that comparing patients with antibiotic-resistant and antibiotic-susceptible infections could lead to overestimation of the role of antibiotic therapy [8]. Following logistic regression analysis, the presence of a central venous catheter (CVC), a history of MRSA infection or colonisation in the previous year, transfer from long-term care facilities or nursing homes, and previous antibiotic therapy were associated significantly with bacteraemia caused by MR-CoNS at hospital admission. The strongest predictor was the presence of a CVC, which increased the risk for bacteraemia by 15-fold. All of the risk-factors identified seemed to be associated with healthcare facilities. Fig. 1 shows the probability of methicillin resistance among patients with true coagulase-negative staphylococcal bacteraemia at hospital admission and during the entire period of hospitalisation. The probability of methicillin resistance among CoNS causing bacteraemia at hospital admission was 73%. After stratification of patients according to admission from the community vs. healthcare facilities, the probability of methicillin resistance among the isolates of CoNS was 62% in patients coming from the community, and 84% in patients coming from other healthcare facilities. Resistance to methicillin was significantly higher among nosocomial isolates of CoNS (73% vs. 88%). Isolates from patients with bacteraemia caused by MR-CoNS at hospital admission were also significantly more likely to be susceptible to gentamicin (63% vs. 44%), clindamycin (49% vs. 27%) and erythromycin (26% vs. 13%) than were those from patients with nosocomial bacteraemia caused by MR-CoNS. All isolates were susceptible to vancomycin. The only risk-factor for methicillin-susceptible coagulase-negative staphylococcal bacteraemia was the presence of a CVC. Other potential risk-factors, including residence in a long-term care facility or nursing home, previous antibiotic therapy or numerous hospitalisations, all of which are associated commonly with antibiotic-resistant pathogens, were not associated with methicillin-susceptible coagulase-negative staphylococcal bacteraemia.

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Given the high prevalence of methicillin resistance among patients with bacteraemia caused by CoNS at hospital admission, further understanding of the epidemiology of such bacteraemia would require knowledge of the mechanisms of dissemination of MR-CoNS, and the ability to distinguish between endogenous and exogenous acquisition. A better knowledge of the epidemiological characteristics of MR-CoNS at hospital admission would help clinicians in choosing empirical therapy, in particular with regard to the use of vancomycin.

**METHICILLIN-RESISTANT S. AUREUS**

Although considered previously to be purely a nosocomial pathogen, recovered from hospitalised patients only, MRSA is now isolated with increasing frequency at hospital admission [9]. These ‘community-acquired’ MRSA strains arise from two different patient populations: first, patients with true community-acquired MRSA strains that have emerged *de novo* from community-based *S. aureus* strains in specific populations (e.g., children, prison inmates and military personnel); and second, patients with healthcare-associated strains that have been acquired during a recent exposure to a healthcare setting or following surgical procedures [10,11]. The latter patient population is twice as likely to harbour MRSA than are individuals without exposure to a healthcare setting [12]. This changing epidemiology has led to an increase in the number of patients with MRSA infections or colonisation diagnosed at hospital admission. A meta-analysis of MRSA infections identified within 24–72 h of hospitalisation documented a prevalence of community-acquired MRSA infections, defined as patients with no known risk-factors for harbouring MRSA, of $\leq 0.24\%$ [13]. These true community-acquired MRSA strains are associated frequently with skin infections, particularly in children, tend to be susceptible to more antibiotics, and are genetically distinct from healthcare-associated strains [14]. In elderly populations, two prospective case-control studies derived risk scores that estimated the likelihood of unknown MRSA carriers at hospital admission [15], with the risk-factors being recent antibiotic therapy, in-hospital transfers, and hospitalisation within the previous 2 years.

To better define risk-factors for healthcare-associated MRSA bacteraemia in adult populations, a case-control study was performed [16]. Using logistic regression analysis, independent risk-factors associated with MRSA bacteraemia at hospital admission included a history of previous MRSA colonisation or infection within 90 days, the presence of a CVC, and skin ulcer or cellulitis at hospital admission. To extend the clinical application of the study results, a second analysis was performed that excluded previous MRSA colonisation or infection, since knowledge of this may not always be available at the time of hospital admission. In this second analysis, although the presence of a CVC was once again
a risk-factor, previous hospitalisations, diabetes mellitus and quinolone therapy were also associated with MRSA bacteraemia at hospitalisation (Table 1). The differences between the two analyses suggest that a previous history of MRSA colonisation or infection may be an indicator of the other risk-factors identified in the second analysis, all of which have been recognised previously to increase the likelihood of MRSA being harboured [17].

The simple patient characteristics identified in the above study can be obtained easily during the clinical assessment of a patient at hospital admission, and can identify a subgroup of patients who are at high risk of MRSA bacteraemia among all the patients admitted from community settings or who have recently had exposure to healthcare intervention. Empirical use of vancomycin in this group may be warranted when patients present with symptoms and signs consistent with bacteraemia. This group of patients may also warrant prompt institution of infection control interventions to limit cross-transmission, since it is well-documented that colonised patients are the chief source of *S. aureus* in hospitals.

Another important factor related to MRSA infections is the availability of a therapeutic agent for the prevention of *S. aureus* colonisation. Mupirocin is a topical antibacterial ointment that has demonstrated efficacy in eradicating colonisation with *S. aureus* [18,19]. In contrast, its efficacy in preventing *S. aureus* infections is controversial, especially following gastrointestinal surgery and for transplant patients [20,21]. Discordant results among published studies, and varying estimates of the risk reduction, may be caused by differences in study design and patient populations, including type of dialysis modality, mupirocin regimen, and type and definition of infection. There are also concerns regarding the emergence of mupirocin resistance among *S. aureus* isolates [22].

A systematic review of the English language literature was performed to determine the overall benefit of mupirocin therapy in reducing the rate of *S. aureus* infection among high-risk patients requiring chronic haemodialysis and peritoneal dialysis [23]. In the year 2000, 71% of dialysis units reported at least one patient with an MRSA infection [24]. Of even more concern are the recent reports of *S. aureus* isolates resistant to vancomycin and linezolid, which have been recovered from chronic haemodialysis patients [25,26]. The following criteria were used in selecting studies for inclusion: studies involving adults aged ≥18 years who required haemodialysis or peritoneal dialysis; randomised controlled clinical trials or cohort studies; use of mupirocin therapy among the treatment group, and a placebo or no therapy among the control group; and a primary outcome showing the difference in the rate of *S. aureus* infections (bacteraemia, exit site infection or peritonitis) between mupirocin-treated and -untreated dialysis patients. In total, ten clinical studies were evaluated, with 1212 patients in the treatment group and 1233 in the control group. Overall, mupirocin therapy reduced the risk of developing *S. aureus* infection by 68% among all dialysis patients (Fig. 2). In a subgroup analysis of different dialysis modalities, the reduction in risk was 80% for haemodialysis patients and 63% for peritoneal dialysis patients, respectively. Analysis of other types of *S. aureus* infection, including exit site infection, peritonitis and bacteraemia, demonstrated significant reductions in risk among patients receiving mupirocin therapy.

This meta-analysis quantified the benefit of mupirocin in preventing *S. aureus* infection in dialysis patients. Nevertheless, the optimal strategy for using this topical antimicrobial agent and minimising the emergence of resistance is still unclear. Since patients often become re-colonised with *S. aureus* following initial treatment, periodic screening, with application of mupirocin for carriers, seems to be a reasonable strategy which would target mupirocin for use with high-risk patients and limit unnecessary use,

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**Table 1. Risk-factors associated with healthcare-associated bacteraemia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) within 24 h of hospitalisation, including (first model) and excluding (second model) a history of previous MRSA infection or colonisation**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MRSA infection or colonisation</td>
<td>17.04 (4.98–58.27)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cellulitis at hospital admission</td>
<td>4.27 (1.52–11.94)</td>
<td>0.006</td>
</tr>
<tr>
<td>Presence of a central venous catheter</td>
<td>3.30 (1.71–6.38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Skin ulcers at hospital admission</td>
<td>3.12 (1.37–7.11)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Second model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of a central venous catheter</td>
<td>3.24 (1.76–5.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospitalisation in the previous 6 months</td>
<td>2.01 (1.11–3.65)</td>
<td>0.02</td>
</tr>
<tr>
<td>Quinolone therapy in the previous 30 days</td>
<td>1.99 (1.07–3.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.84 (1.05–3.22)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adapted from Tacconelli et al. [16].

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thereby decreasing the emergence of resistance. Future studies in other high-risk populations are needed.

VANCOMYCIN-RESISTANT ENTEROCOCCI

VRE have become endemic in numerous healthcare institutions in Europe and the USA [27,28]. A 1-day cross-sectional study in a 1700-bed university hospital in Rome, with 60 000 admissions annually, found 25 patients colonised with VRE/1000 admissions [29]. The recent isolation of vancomycin-resistant S. aureus strains, resulting from the transfer of vancomycin resistance genes from VRE to S. aureus [30,31], emphasises the urgent need to prevent de-novo acquisition of VRE. Impeding the influx of VRE into a healthcare institution would require a programme of active surveillance, using cultures to detect gastrointestinal colonisation with VRE among all patients admitted to the hospital. However, given the low prevalence of VRE at admission, it would not be economically feasible to screen all newly admitted patients.

To identify the characteristics of patients at high risk for colonisation with VRE, a two-centre, 6-year study of patients harbouring VRE at hospital admission was performed [32]. From this analysis, a clinical prediction rule was developed to indicate which high-risk subgroup of newly admitted patients required screening for VRE and contact isolation. The prediction rule was then validated using a separate cohort of high-risk patients. Six variables, easily obtainable during the initial clinical assessment of patients, were identified and weighted scores were applied. The variables identified were: age > 60 years; hospitalisation during the previous year; use of two or more antibiotics during the previous 30 days; transfer from another hospital or long-term care facility; a requirement for chronic haemodialysis; and a previous history of MRSA colonisation or infection. To develop the prediction rule, a scoring system using point values was employed. The natural logarithm of the odds ratio of each risk-factor selected by the logistic regression model was multiplied by two and rounded off to the nearest integer (Table 2). With a point score cut-off of ≥10, the specificity of this prediction rule was 98% in the combined derivation and validation cohorts (Fig. 3). The predictive values were similar in both cohorts of study patients from two different hospitals, further validating the accuracy of the prediction rule. These results

<table>
<thead>
<tr>
<th>Risk-factor</th>
<th>Points score</th>
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<tbody>
<tr>
<td>MRSA colonisation or infection</td>
<td>4</td>
</tr>
<tr>
<td>within the previous year</td>
<td></td>
</tr>
<tr>
<td>Chronic haemodialysis</td>
<td>3</td>
</tr>
<tr>
<td>Long-term facility/hospital transfer</td>
<td>3</td>
</tr>
<tr>
<td>Exposure to two or more antibiotics within the previous 30 days</td>
<td>3</td>
</tr>
<tr>
<td>Hospitalisation within the previous year</td>
<td>3</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus.
Adapted from Tacconelli et al. [32].

Table 2. Risk index for vancomycin-resistant enterococci at hospital admission
suggest that use of this prediction rule (i.e., a points score of $\geq 10$) with patients at hospital admission would identify a large proportion of patients harbouring VRE correctly. Fig. 4 displays the positive and negative predictive values for the scoring system when comparing patients with VRE at hospital admission and patients without VRE in derivation and validation cohorts.

Screening programmes for detecting VRE among patients who are already hospitalised have been used extensively [33,34]. These programmes are based on the important premise that for every patient from whom VRE are recovered in clinical cultures, there are many more patients who have unrecognised colonisation with VRE [35]. Tremendous benefit from screening programmes has been achieved by decreasing the overall prevalence of VRE and the number of infections with VRE over time [36,37]. The cost-effectiveness of this approach has also been demonstrated [35,36]. The risk score approach appears to be a novel and diagnostically accurate strategy for potentially preventing dissemination of VRE from the reservoir of VRE entering the hospital, thereby ultimately decreasing cross-transmission and de-novo acquisition of VRE.

**CONCLUSIONS**

Preventing transmission of antibiotic-resistant bacteria is important, since these infections are associated with considerable morbidity and mortality, and excess hospital costs. Rising rates of methicillin-resistant staphylococcal infections also result in greater use of vancomycin, with an increased risk of emergence of glycopeptide-resistant pathogens. Knowledge of the variables that identify patients at higher risk for being carriers, or for being infected with antibiotic-resistant bacteria, may assist clinicians in targeting preventive measures and streamlining the use of vancomycin.
Until now, most prevention strategies in hospitals have targeted the middle component of the endemic state, i.e., cross-transmission among hospitalised patients. However, many studies have now shown the importance of the influx of antibiotic-resistant bacteria into hospitals. Epidemiological studies are therefore necessary to understand the variables associated with a high risk for being colonised or infected with antibiotic-resistant bacteria at hospital admission. In particular, the clinical prediction rule described above for VRE provides an additional strategy for targeting the influx of the microorganism into a hospital by identifying patients harbouring VRE at hospital admission. This strategy would limit the potential for dissemination of VRE from these unrecognised reservoirs at the start of their period of hospitalisation, as opposed to other strategies, in which screening programmes target patients already hospitalised. Although the influx of VRE into a hospital would not change, the benefit of early detection is that it would reduce the time that such unrecognised carriers might have to disseminate VRE. The spread of antibiotic-resistant bacteria within a hospital is a complex process. Elucidating and intervening at all stages of the transmission chain may allow the use of more weapons to win this fight.

ACKNOWLEDGEMENTS

This review was based on an ESCMID Award Lecture presented at the 15th European Congress on Clinical Microbiology and Infectious Diseases (Copenhagen, 2004). The studies described in this review were performed in the Departments of Infectious Diseases at the Catholic University (Rome, Italy) and at BIDMC, Harvard Medical School (Boston, USA). R. Cauda, A. W. Karchmer and E. M. D’Agata are thanked for their contribution to the studies presented in this review.

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