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Impact of inappropriate empirical therapy for sepsis due to health care-associated methicillin-resistant *Staphylococcus aureus*

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Summary *Objectives:* We investigated the influence of empirical therapy on the mortality of patients with health care-associated (HCA) sepsis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) infections in a multicenter cohort, and the variables associated with inappropriate empirical therapy.
Methods: All new cases of infection caused by HCA-MRSA presenting with sepsis syndrome in 59 Spanish hospitals during June 2003 were prospectively followed. The main outcome variable was mortality at day 30. Predictors of mortality and of inappropriate empirical therapy were studied using multivariate logistic regression.
Results: We included 209 cases. Crude mortality was 23%. After controlling for severity of the underlying condition, ICU stay, presentation with severe sepsis or shock, and site of infection, inappropriate empirical therapy was associated with an increased odds of mortality (OR = 3.0; 95% CI: 1.01–9.0; $p = 0.04$). Only 21.1% of the patients received appropriate empirical therapy. Variables independently associated with appropriate therapy were recent surgery, central venous catheter and certain sites of infection (primary bacteraemia, intraabdominal infections, and respiratory tract infections). Cancer patients were at an increased risk of receiving inappropriate therapy.

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Conclusions: Inappropriate empirical therapy was independently associated with increased mortality in this multicenter cohort. Clinicians should be aware of the need to consider coverage against MRSA more frequently.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important health care-associated (HCA) pathogens. Even though the emergence of community-acquired (CA) clones of MRSA has been receiving most of the attention recently, HCA-MRSA is by far a more frequent cause of invasive disease than CA-MRSA.[1] Infections caused by this organism are associated with substantial morbidity and, in the case of invasive infections (such as primary bacteraemia, endocarditis or pneumonia), with increased mortality in comparison to methicillin-susceptible (MS) *S. aureus*.[2]

Since there is no compelling evidence that HCA-MRSA is more virulent than MSSA,[3,4] and MRSA-associated mortality is still higher when the underlying condition of the patients is controlled,[2] the worse prognosis of MRSA infections has been related to therapeutic problems. Since these organisms are frequently multi-drug resistant, antimicrobial treatment of infections caused by MRSA is frequently inappropriate.[5,6] The impact of appropriate empirical therapy on the survival of patients with bacteraemia or other sterile-site infections due to MRSA is controversial.[6–11] Also, glycopeptides (the traditional agents of choice for treating MRSA) are recognised to be less effective than β-lactams against susceptible *S. aureus*.[12]

The aims of this study were to describe the outcome of sepsis caused by HCA-MRSA in several Spanish hospitals, and to analyse the impact of empirical therapy in the outcome.

Patients and methods

This study is part of the SARM 2003 GEIH/GEMARA/REIPI project, aimed at investigating the epidemiology, clinical features and microbial characteristics of MRSA infection and colonisation in Spain. Some epidemiologic and microbiologic analyses of the data have been reported elsewhere.[13,14] The 59 participating hospitals provide health care coverage for >10 million inhabitants. Distribution regarding the number of beds was: <200 beds, 24%; 200–500 beds, 35%; and >500 beds, 40%. Active transplantation programs were developed in 37%, and 76% had an intensive care unit. The project included a prospective cohort study, in which all new cases of colonisation or infection due to HCA-MRSA occurring during June 2003 in the participating hospitals were prospectively followed for 30 days. Data were recorded by clinical and microbiologic investigators at each participating hospital.

All adult (>14 years) patients from the cohort were considered potentially eligible for this analysis. Patients were included in this analysis if all the following criteria were satisfied: MRSA was considered to be causing an infection (as defined below), MRSA was considered HCA, and the patient was considered to have sepsis at the time of the study entry. All patients were hospitalised. Information regarding the following variables was collected for all patients: age, gender, comorbidities, severity of the underlying disease, nosocomial onset, invasive procedure performed during the last 3 months, previous antimicrobial therapy, presence of infection and sites of infection, presentation with severe sepsis or septic shock, appropriate antimicrobial treatment, hospital size and MRSA rate during the previous year as previously reported.[13] The outcome variable was 30-day mortality. Length of hospital stay after the infection was also collected. The project was approved by the local ethics committees.

Definitions

The Charlson index[15] was used to assess the severity of the underlying conditions. Patients were considered to be infected according to CDC criteria, which were also used to establish the site of infection[16]; otherwise, the patients were considered to be colonised and excluded. Community-onset infections (those occurring in outpatients, or in inpatients with ≤48 h of hospital admission) were considered HCA if during the previous year the patient had any of the following: hospital, nursing home or other health care facility admission for >2 days, surgery, dialysis, specialised home care, attention at day hospitals, or permanent indwelling catheters. Otherwise, they were considered CA and excluded; epidemiological criteria were further assessed by analysing the microbiological features of the isolates using recently proposed criteria.[17] Infections occurring in inpatients after 48 h of hospital admission were considered as nosocomial. Sepsis, severe sepsis, and septic shock were defined according to standard criteria.[18] Antimicrobials administered before the susceptibility data were known (typically, in the first 48–72 h after the culture had been performed) were considered empirical. Empirical therapy was considered appropriate whenever an active antimicrobial agent (according to *in vitro* data) had been administered at standard doses and by the recommended route for at least 24 h during the first 48 h after the culture had been obtained; if the only active drug was an aminoglycoside, the treatment was considered inappropriate. Therapy administered once the susceptibility results were known was considered definitive.

Microbiologic studies

Preliminary identification and susceptibility testing were initially performed in each hospital. Isolates were sent to the reference laboratory (Hospital de Bellvitge, Barcelona). Identification of the isolates was confirmed by biochemical tests. Antibiotic susceptibility was studied by the disc-diffusion method and methicillin resistance was confirmed by the E-test and detection of the *mecA* gene by PCR.

Statistical analysis

Continuous variables were compared by the Student t test or the Mann–Whitney U test as appropriate, and qualitative ones by a chi squared test (Fisher exact test if required). Unadjusted relative risks (RR) with 95% confidence intervals (CI) were calculated. Multivariate analyses were performed by stepwise logistic regression analysis, and the adjusted odds ratios (OR) with 95% CI were provided. Since our main objective was to investigate the impact of appropriate empirical therapy, a multivariable model was constructed using a forward stepwise method; the first variable introduced was empirical therapy, and other variables with a p value of <0.1 from the univariate analysis were then added step by step. For the exploratory analysis of factors associated with inappropriate empirical therapy, variables were selected using a stepwise backward approach. The SPSS software package was used.

Results

During the study period, MRSA was isolated from 370 patients in the participating hospitals; 118 patients were considered to be only colonised, three cases were considered CA, and 40 patients did not present with sepsis. Thus, 209 patients were included. The features of the patients are shown in Table 1. Among the 145 nosocomial infections, 61 patients were admitted to medical services, 57 to surgical services, and 27 to ICUs, and their median (interquartile range) previous stay was 13 days (5–25).

The sites of infections are also shown in Table 1. Overall, 62 patients (29.7%) were bacteraemic. Infection, regardless of the site, was considered as surgical-related in 57 (27.7%) patients. Eight patients (3.8%) presented with severe sepsis and 11 (5.2%) with septic shock. Mortality at day 30 was 23.0% (48 patients). Death occurred in the first 7 days after the infection was diagnosed in 20 patients (41.6% of deaths). Median hospital stay after the infection in survivors was 18 days (interquartile range, 10–30). Empirical antimicrobial therapy was administered to 192 patients (93%).

Mortality was <15% for skin and soft tissue infections, urinary tract infections, arthritis/osteomyelitis and miscellaneous infections, and >25% for primary bacteraemias, respiratory tract infections and intraabdominal infections. Thus, the category ''type of infection'' was reclassified into a dichotomous variable (low- and high-risk sites of infection) to facilitate the control for this variable in the multivariate analysis. The univariate analysis of variables associated with the 30-day mortality is shown in Table 2. Only 44 patients (21.1%) received appropriate empirical antimicrobial therapy; the active agents received were glycopeptides (37 patients), trimetoprim–sulfamethoxazole (5), and clindamycin (2); six of them also received an active aminoglycoside. The 30-day mortality was 24.2% (40 patients) for the 165 patients who received inappropriate empirical therapy and 18.2% (eight patients) for the 44 patients who received appropriate empirical therapy (RR = 1.3; 95% CI: 0.6–2.6; $p = 0.3$). Stratified analysis indicated that the effect of empirical therapy was subject to confusion bias by the effect of other variables. In the multivariate analysis, after controlling for Charlson index >2, ICU stay, presentation with severe sepsis or septic shock, and high-risk source, appropriate empirical therapy was found to be associated with lower mortality (Table 2). Definitive therapy was not associated with mortality. We also performed models testing interactions (empirical therapy and high or low-risk sites, empirical therapy and presentation with severe sepsis or septic shock), but none of the interactions were associated with outcome. We repeated all the analyses, excluding the four patients who died within 2 days of the sample being taken; the results did not change significantly (data not shown). Of the 151 patients who received inappropriate empirical therapy but survived until the susceptibility results were available, 121 received appropriate definitive therapy, and 23 (19%) died; 30 patients did not receive appropriate definitive therapy, and eight (26.7%) died ($p = 0.3$). After controlling for other variables, definitive therapy remained non-significantly associated with outcome (data not shown).

Table 1 Features of 209 patients hospitalised with health care-associated infections caused by methicillin-resistant *S. aureus*. Data are expressed as no. of cases (percentage) except where indicated.

Male gender	124 (59.3)
Median age in years (interquartile range)	71 (60–77)
Charlson index >2	145 (59.1)
Comorbidity	
Diabetes mellitus	74 (35.4)
Chronic pulmonary disease	46 (22.0)
Liver cirrhosis	12 (5.7)
Malignancy	48 (23.0)
Renal insufficiency	21 (10.0)
HIV infection	4 (1.9)
Onset of infection	
Community[a]	64 (30.6)
Nosocomial	145 (69.4)
Predisposing factors	
Central venous catheter	57 (27.3)
Urinary catheter	67 (32.1)
Mechanical ventilation	26 (12.4)
Surgery (during previous month)	78 (37.3)
Previous antimicrobial treatment (previous month)	153 (73.2)
Site of infection	
Skin and soft tissue	89 (42.6)
Primary bacteraemia/ catheter-related infection	33 (15.8)
Pneumonia	22 (10.5)
Other respiratory tract infection	21 (10.0)
Urinary tract infection	16 (7.7)
Arthritis/osteomyelitis	14 (6.7)
Intraabdominal infection	7 (3.3)
Others	7 (3.3)

MRSA: methicillin-resistant *Staphylococcus aureus*.
[a] All cases were health care-associated.

Table 2 Univariate and multivariate analyses of factors associated with mortality at day 30 among patients with infections due to methicillin-resistant *S. aureus*.

Variable	Category	No. of deaths (percentage)	*p* value	Multivariate OR (95% CI)	*p* value
MRSA rate during last year (cases per 1000 patient-days)	<0.5	31 (22.1)	0.5	—	—
	≥0.5	17 (25.8)			
Number of beds	>200	35 (21.1)	0.2	—	—
	≤200	13 (30.2)			
Age >60 years	Yes	35 (23.0)	0.9	—	—
	No	13 (22.8)			
Gender	Male	31 (25)	0.4	—	—
	Female	17 (20.2)			
Charlson index >2	Yes	32 (32)	<0.001	3.4 (1.5–7.6)	0.001
	No	16 (11.1)			
ICU	Yes	14 (51.9)	<0.001	4.2 (1.4–12.4)	0.009
	No	34 (18.7)			
Onset[a]	Nosocomial	34 (23.4)	0.8	—	—
	Community	14 (21.9)			
High-risk site[b]	Yes	30 (36.1)	<0.001	2.9 (1.3–6.5)	0.007
	No	18 (14.3)			
Bacteraemia (primary or secondary)	Yes	16 (25.8)	0.5	—	—
	No	32 (22.1)			
Severe sepsis or septic shock at presentation	Yes	13 (68.4)	<0.001	7.5 (2.3–23.9)	<0.001
	No	35 (18.4)			
Empirical therapy	Inappropriate	40 (24.2)	0.3	3.0 (1.01–9.0)	0.04
	Appropriate	8 (18.2)			
Definitive therapy[c]	Inappropriate	8 (22.2)	0.5	—	—
	Appropriate	30 (18.4)			

[a] All were health care-associated.
[b] High-risk site infections include primary bacteraemias, respiratory tract infections, and intraabdominal infections.
[c] Ten patients who died before the susceptibility tests were available were excluded.

Then, we analysed the variables associated with the probability of receiving appropriate empirical therapy. Considering the site of infection, the frequency of appropriate empirical therapy was: intraabdominal, 42.9%; primary bacteraemia/catheter-related, 36.4%; respiratory, 27.9%; arthritis/osteomyelitis, 21.4%; skin and soft tissue, 14.6%; urinary tract, 6.3%; and miscellaneous, 0. We classified the sites of infection into those with a >25% probability of receiving appropriate therapy (intraabdominal, primary bacteraemia/catheter-related, and respiratory infections) and those with <25% probability. The results of the univariate and multivariate analyses are shown in Table 3. Patients with bacteraemia received appropriate therapy more frequently than patients without bacteraemia (29% vs 17.2%, $p = 0.05$), but this variable was not introduced in the multivariate analysis because clinicians do not know which patients are bacteraemic when initiating empirical therapy.

Discussion

The burden and clinical importance of invasive MRSA disease are enormous: a recent study performed in the US found a standardised incidence rate for MRSA invasive infections of 31.8 cases per 100 000 persons during 2005; the mortality rate in that study was 19% (18 650 deaths among 94 360 cases).[1] Even though CA-MRSA has emerged during the last decade as an important pathogen in some areas, HCA-MRSA outnumber CA-MRSA even in areas where CA-MRSA is prevalent.[1] Only a few cases of infections caused by CA-MRSA have been described in Spain so far.[14,19–21] Thus, we focused our study on HCA-MRSA. The impact of appropriate empirical therapy against MRSA on survival has been explored in several studies including only patients with bacteraemia; their results were contradictory.[6–10] To the best of our knowledge, only one other study has evaluated the importance of empirical therapy in other types of infection[11]; in that particular study, which included patients with sterile-site infections, inappropriate therapy was associated with increased mortality. All previous studies were carried out in one center. We analysed the influence of inappropriate empirical therapy on the outcomes of diverse infections presenting with sepsis syndrome caused by HCA-MRSA, and which included cases from a wide sample of hospitals. After controlling for the infection site, the underlying condition, and the severity of presentation, we found that inappropriate empirical therapy was associated with increased mortality.

We selected 30-day mortality as our outcome variable. One limitation of such a variable is that an important factor in mortality might be the underlying condition of the patients, reflected in the significance of the Charlson index, rather than the infection itself, and underestimating,

Table 3 Univariate and multivariate analyses of variables associated with appropriate empirical therapy in patients with infections due to MRSA.

Variable	Category	No. of patients with appropriate therapy (percentage)	*p* value	Multivariate OR (95% CI)	*p* value
MRSA rate during last year (cases per 1000 patient-days)	<0.5	30 (22.3)	0.9	—	
	≥0.5	14 (21.2)			
Number of beds	>200	36 (21.7)	0.6	—	
	≤200	8 (18.6)			
Age >60 years	Yes	31 (20.4)	0.7	—	—
	No	13 (22.8)			
Gender	Male	27 (21.8)	0.7	—	—
	Female	17 (20.2)			
Charlson index >2	Yes	14 (15.2)	0.06	—	—
	No	30 (25.6)			
Chronic renal insufficiency	Yes	7 (33.3)	0.1	—	—
	No	37 (19.7)			
Cancer	Yes	5 (10.4)	0.03	0.2 (0.08—0.7)	0.01
	No	39 (24.2)			
ICU	Yes	13 (48.1)	<0.001	—	—
	No	31 (17)			
Onset	Nosocomial	34 (23.4)	0.2	—	—
	Community	10 (15.6)			
Intraabdominal, primary bacteraemia or respiratory tract infection	Yes	27 (32.5)	0.001	2.6 (1.1—5.9)	0.01
	No	17 (13.5)			
Central venous catheter	Yes	22 (38.6)	<0.001	2.1 (0.93—4.8)	0.07
	No	22 (14.5)			
Mechanical ventilation	Yes	10 (38.5)	0.02	—	—
	No	34 (18.6)			
Surgery	Yes	23 (29.2)	0.02	2.5 (1.1—5.7)	0.01
	No	21 (16)			
Previous antimicrobial therapy	Yes	37 (24.2)	0.04	—	—
	No	6 (11.1)			
Severe sepsis or septic shock	Yes	5 (26.3)	0.5	—	—
	No	39 (20.5)			

therefore, the impact of variables relating to the infection, in particular, the importance of empirical therapy. In fact, inappropriate empirical therapy was not associated with mortality in the univariate analysis, because of the confusion bias produced by other variables. However, the fact that empirical therapy was associated with outcome in the multivariate analysis strongly suggests that it is an important determinant of outcome in sepsis due to MRSA. We decided not to use infection-related mortality, as this variable is subject to investigator bias which may be particularly frequent in multicenter studies. Finally, a retrospective analysis using 7-day mortality as the outcome variable could not be performed since only 21 patients died within the first 7 days, which limited the number of variables for inclusion in a multivariate analysis to two.[22]

Vancomycin accounted for the majority of appropriate regimens. However, it should be remembered that vancomycin is not an optimum drug for the treatment of serious methicillin-susceptible *S. aureus* infections, since it has been shown to be associated with worse outcomes than β-lactams in the treatment of bacteraemia due to susceptible isolates.[12] Nevertheless, no other antimicrobial has yet been demonstrated to be unequivocally superior against MRSA, and according to our data and those by other authors,[10] empirical vancomycin is better than administering no active agent. Although our results might suggest that the impact of changing therapy on patients who had received inappropriate empirical antimicrobials may be limited in terms of mortality, we think that this should be interpreted with caution; since the number of patients with inappropriate definitive therapy was low, it is probable that our study had insufficient statistical power to detect the impact of the definitive therapy. Moreover, we did not evaluate other outcome variables, such as the length of stay or recurrence, which are probably influenced by definitive therapy.

Our study has several limitations. We did not consider the MIC of vancomycin, since the prognosis of patients with bacteraemia due to MRSA treated with vancomycin has been shown to be worse when the MIC of the isolate was >1 mg/L.[10] Also, we did not collect data about the trough levels of vancomycin, which might be necessary for the

treatment of susceptible isolates with high MIC,[23] although this is a controversial issue. Even though we used simple, standard criteria to define variables, some variability may have occurred when applying the criteria in the participating centers, as in all multicenter studies. The short study period (1 month) is another limitation; however, since many hospitals participated, it allowed to perform a careful evaluation and follow-up of each case. Finally, most appropriate empirical regimens included vancomycin, although some patients received other agents; since the number of patients receiving these other agents was low, we were unable to evaluate their role in the outcome.

In our study, appropriate empirical therapy was administered only to 21% of the patients. In a previous study including patients with sterile-site infections, only 25.8% of 549 patients received appropriate empirical therapy.[11] Studies including only patients with bacteraemia found 24—59% of appropriate empirical therapy[5—10]; we found that 29% of bacteraemic patients in our series received appropriate empirical therapy, which was significantly higher than what happened with non-bacteraemic patients. Whatever the case, the low frequency of appropriate empirical therapy among patients with serious infections due to MRSA underscores the paradoxical fact that even though this is a frequent HCA pathogen, clinicians are still reluctant to include it in the empirical coverage.

Several factors might contribute to this: first, the frequency of MRSA may still be underestimated by some clinicians; second, this might be an adverse effect of the restriction policies in the use of vancomycin as a consequence of the problem posed by vancomycin-resistant enterococci, or (if an alternative to vancomycin is sought) in the use of newer drugs active against MRSA (linezolid, daptomycin) due to their high cost; and third, some clinicians may have the perception that inappropriate empirical therapy does not influence the outcome in MRSA infections. In our study, appropriate empirical therapy was more frequent in cases of recent surgery, presence of a central venous catheter, and certain sites of infection (intraabdominal infections, primary bacteraemia/catheter-related infections, and respiratory tract infections). Curiously, cancer patients were at a higher risk of receiving inappropriate empirical therapy. Although the frequency of appropriate empirical therapy in patients with community-onset HCA infections and nosocomial infections was similar in our study, community-onset HCA bacteraemia due to MRSA has been associated with inappropriate empirical therapy in another study.[24]

The investigation of predictive variables for MRSA infection may help clinicians to decide when it is necessary to cover MRSA, but the risk factors found can be unspecific,[25] and local differences in the epidemiology might make the translation of such data into clinical practice difficult. Previous MRSA colonisation is a well-recognised risk factor for the subsequent development of MRSA invasive infection.[26,27] We expect that a wider implementation of active surveillance to detect patients colonised with MRSA as a means of controlling the spread of the organism[28] will also be of help to improve the empirical therapy of these patients. Providing patients with serious MRSA infections the appropriate empirical therapy is a clinical challenge.

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