Title: Clinical and economic burden of community-onset multidrug-resistant infections requiring hospitalization

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Running title: Community-onset multidrug-resistant infections

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Abstract

Objectives: To analyze the clinical and economic burden of community-acquired (CA) or community-onset healthcare-associated (CO-HCA) multidrug-resistant (MDR) infections requiring hospitalization.

Methods: Case-control study. Adults admitted with CA or CO-HCA MDR infections were considered cases, while those admitted in the same period with non-MDR infections were controls. The matching criteria were source of infection and/or microorganism. Primary outcome was 30-day clinical failure. Secondary outcomes were 90-day and 1-year mortality, hospitalization costs and resource consumption.

Results: 194 patients (97 cases and 97 controls) were included. Multivariate analysis identified age (odds ratio [OR], 1.07, 95% confidence interval [CI], 1.01-1.14) and SOFA score (OR, 1.45, CI95%, 1.15-1.84) as independent predictors of 30-day clinical failure. Age (hazard ratio [HR] 1.09, 95%CI, 1.03-1.16) was the only factor associated with 90-day mortality, whereas age (HR 1.06, 95%CI, 1.03-1.09) and Charlson Index (HR 1.2, 95%CI, 1.07-1.34) were associated with 1-year mortality. MDR group showed longer hospitalization ($p < 0.001$) and MDR hospitalization costs almost doubled those in the non-MDR group. MDR infections were associated with higher antimicrobial costs.

Conclusions: Worse economic outcomes were identified with community-onset MDR infections. MDR was associated with worse clinical outcomes but mainly due to higher comorbidity of patients in MDR group, rather than multidrug resistance.

Key words: multidrug resistance, community-onset infections, community-onset healthcare-associated infections, clinical failure, mortality, resource consumption, hospital costs, burden.

Introduction

Multidrug-resistant (MDR) bacterial infections have become a major public health concern over the last years, being associated with worse outcomes when compared with similar infections caused by susceptible strains¹⁻⁴. They are closely related to delays to effective antibiotic treatment^{2,5}. Furthermore, drugs that are active against MDR infections tend to be less effective and more toxic than conventional agents². Patients with MDR infections are more prone to underlying conditions, which may lead to worse outcomes^{1,3}. Antimicrobial resistance is also becoming a problem in terms of the functioning of healthcare systems and their budgets. A 2015 report estimated that G7 countries could face increased expenditure of about USD 2.9 trillion by 2050 because of MDR infections⁶.

MDR bacteria have traditionally been closely linked to hospital-acquired infections. In recent years however, the spread of these strains in the community has shifted problem beyond the hospital setting⁷. *Wolfe et al.* pointed out that, in Japan, nearly one in three community-onset bloodstream infections was antibiotic-resistant⁸. The increasing incidence of community-acquired infections due to *Escherichia coli* and extended-spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae* is especially concerning^{9,10}. A Spanish national survey observed that approximately 32% and 10% of *E. coli* and ESBL-producing *K. pneumoniae*, respectively, could be considered community-onset infections¹¹. Methicillin-Resistant *Staphylococcus aureus* (MRSA) is another example of the extensive spread of multidrug resistance beyond the hospital setting¹². Although its prevalence has declined in most of Europe¹³, community MRSA infections remain a healthcare problem, particularly since they usually combine resistance to other antimicrobial groups and can occur in healthy individuals without predisposing conditions¹². Carbapenem-resistant bacteria are also an emerging threat with a reported prevalence ranging from 0.04% to 29.5% in community-acquired or community-onset infections¹⁴.

Previous studies have analyzed both the clinical and economic impact of multidrug resistance, although mainly in the context of hospital-acquired infections^{15–17}. In community-onset MDR infections however the burden of antibiotic resistance is not well understood. In addition, past research has mainly centered on specific MDR microorganisms or sources of infection^{5,10,18–23}, shifting the focus away from the global perspective of a global.

The aim of this study is to gain a better understanding of the clinical and economic impact of multidrug resistance in patients with community-onset MDR infections of any source caused by gram-positive or gram-negative MDR strains who require hospital admission.

Patients and methods

Study design

This was a case-control study of patients who were hospitalized for more than 48h following community-acquired (CA) or community-onset healthcare-associated (CO-HCA) infections caused by MDR and non-MDR bacteria. The study was conducted at the Hospital del Mar, a 420-bed tertiary care university hospital in Barcelona (Spain), between January 2015 and December 2016.

All positive cultures requested by the emergency department during this period with significant growth of MDR isolates were retrospectively reviewed. Only patients with clinically relevant infection were included in the study, while patients with MDR isolates but no signs or symptoms of infection were considered as colonized and excluded. A patient was selected as a case when all the following criteria were met: patient aged 18 years or older, culture positive for MDR gram-positive or gram-negative bacteria, presence of symptoms and/or signs of infection at the same source as the MDR bacteria isolation, and CA or CO-HCA infection requiring hospital admission.

Polymicrobial infections and hospital-acquired infections were excluded. Only the first episode of infection per patient was considered.

The control group was selected from patients admitted to hospital from the emergency department with CO or CO-HCA infections during the same period (nearest date). The matching criteria were based on controls and cases having the same source of infection and a susceptible strain of the same microorganism. When the two criteria were applied together, the initial groups were not large enough for the sample size required for statistical analysis (see further), so that the criterion for control inclusion was relaxed to either the same source of infection or a susceptible strain of the same microorganism as the cases. The case-control ratio was 1:1. This study was approved by the Clinical Research Ethical Committee of Parc de Salut Mar (CEIC Parc de Salut Mar, registration n° 2018/7865/I).

Microbiological Data

MDR was defined as resistance to at least one agent in three or more antimicrobial categories for each organism, in accordance with current standard definitions²⁴. MRSA was always considered as MDR.

Routine identification and susceptibility testing of causative microorganisms were performed using automated systems (Vitek-2® [BioMérieux] for blood cultures, and the MicroScan® WalkAway [Beckman-Coulter] for other types of samples) and interpreted according to standards defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Isolates with intermediate antimicrobial susceptibility were considered as resistant. For gram-negative bacilli, ESBLs, plasmid-mediated AmpC β -lactamases and carbapenemases were investigated. ESBL and plasmid-mediated AmpC β -lactamase production was confirmed by the double disc approximation test. Synergy was determined between a disc of amoxicillin-clavulanic acid (20 μ g/10 μ g) and a 30 μ g disc of cefotaxime, ceftazidime and cefepime.

Carbapenemases were identified by multiplex PCR assay, using the LightMix® Modular Carbapenemase panel (Roche Diagnostics). For *S. aureus*, production of PBP2a was confirmed phenotypically by the ceftioxin disk diffusion test (30µg disc).

Data collection and variables analyzed

Clinical data were retrospectively collected from electronic medical charts, and economic data from the hospital financial database. The following variables were recorded: demographic characteristics, underlying diseases according to Charlson Index Score²⁵ and immunosuppression status. Prior hospitalizations, residence in long-term care facility, chemotherapy, home intravenous therapy or wound care in last 30 days, antibiotic exposure and use of invasive devices within the previous three months were recorded. An assessment of clinical severity was made for severe sepsis or septic shock²⁶ and Sequential Organ Failure Assessment (SOFA)²⁷ at presentation, with the Pitt Score in case of bacteremia²⁸. The need for surgery or intensive care unit (ICU) admission in the first 72 hours was also recorded. With respect to antimicrobial treatment, empirical and definitive antimicrobial treatment, time to adequate treatment, duration of antibiotic treatment and side effects were evaluated. With respect to healthcare resource consumption, the following variables were studied: length of stay, outpatient parenteral antibiotic therapy, number of ambulatory visits at 3 months, readmissions at one-year follow-up and overall hospitalization, pharmaceutical, laboratory, imaging and other diagnostic procedure costs.

Definitions

Specific types of infection were defined according to the Centers for Disease Control and Prevention²⁹.

CA infections were defined by *Van Duin et al.* as those occurring in non-hospitalized patients or with onset within the first 48 hours of hospitalization that do not meet any of the criteria for healthcare-associated infections⁷. CO-HCA infections were defined as those occurring in the following situations: the patient had been hospitalized for two or more days in an acute care hospital, or been admitted to a nursing home or long-term care facility within the previous 90 days; or had received home-based intravenous antibiotic therapy, chemotherapy, or wound care within the 30 days preceding the current infection; or had visited a hospital or hemodialysis clinic³⁰.

Severe sepsis was considered if there was at least one organ failure, whereas septic shock was defined as the need for vasopressors to maintain a mean arterial pressure of at least 65 mmHg²⁶. Antibiotic treatment was considered appropriate when it included at least one antibiotic active *in vitro* against the isolated microorganism. Time to adequate antibiotic treatment was defined as number of days between a positive culture and appropriate empiric or definitive treatment. Clinical failure was defined as the persistence or worsening of initial infectious symptoms, or the need to maintain antibiotic treatment 30 days post-admission.

With respect to resource consumption, both all-cause and infection-related outpatient visits and readmissions were considered. Infection-related follow-up events were defined as unplanned visits subsequent to the index admission to evaluate a current infection, or readmission due to relapse or reinfection.

Overall cost of hospitalization was defined as medical services received during the entire hospital admission and included the cost of pharmaceuticals (antibiotic treatment and other drugs, fluids, nutritional supplements), laboratory services (chemistry, blood

count, microbiological cultures), imaging and other diagnostic procedures (computerized tomography scan, magnetic resonance imaging scan, echography, endoscopy).

Outcomes

Differences in clinical outcome between MDR and non-MDR infections were evaluated through an assessment of clinical failure at day 30 (primary endpoint). Secondary outcome measures included: 90-day and 1-year all-cause mortality and costs of hospitalization (total cost of the episode and costs attributable to antibiotic treatment).

Statistical analysis

Determining the sample size required (194 patients) was based on the results of a previous study¹⁸ to detect a 15% difference in clinical response between MDR and non-MDR infections; statistical power was set at 80% and alpha error at 0.05.

Categorical variables were presented as number of cases and percentages, and continuous variables as median and interquartile range (IQR). The Student's t-test or Mann-Whitney U test were used to compare continuous variables, and Pearson's chi-squared or Fisher's exact test to compare categorical variables, as appropriate. A logistic regression model using backward stepwise selection examined independent variables associated with clinical failure at day 30. Results were expressed as odds ratio (OR) and 95% confidence interval (CI). Kaplan-Meier survival curves and the log-rank test were used to determine 1-year mortality differences between MDR and non-MDR infections. The Cox proportional hazards model was used to perform multivariate survival analyses of 90-day and 1-year all-cause mortality and results were reported as hazard ratio (HR) and 95%CI. Multivariate analysis included clinically relevant variables and/or those with p value <0.1 in univariate analysis. Economic impact was evaluated

by median regression to deal with lack of normality of dependent variables (costs of hospitalization). Results were expressed as difference of medians (DM). The interpretation of coefficients was as for the interpretation of coefficients in multiple linear regression, based on the difference of means. All p-values were 2-tailed and statistical significance was <0.05. Statistical analyses were performed using STATA 15.

Results

During the study period, 194 patients fulfilling the inclusion criteria were studied: 97 infections were due to MDR microorganisms (cases) and 97 to non-MDR microorganisms (controls). Overall, the most frequently isolated microorganisms were *E. coli* (n=102), *Klebsiella* spp. (n=25), and *S. aureus* (n=24) (Figure 1). Among MDR Enterobacteriaceae, the most commonly observed pattern was ESBL production [a total of 61 ESBL carriers; 49/55 (89%) MDR *E. coli*, 11/13 (85%) MDR *Klebsiella* spp and 1/1 *Enterobacter cloacae*]. Of the 61 ESBL isolates studied, 55 (90.2%) were resistant to amoxicillin-clavulanic acid, 50 (82%) to fluoroquinolones, 48 (78.7%) to trimethoprim-sulfamethoxazole, 42 (68.9%) to aminoglycosides and 36 (59%) to piperacillin-tazobactam. More than 90% (n=41/45) of ESBL producers tested for fosfomycin were susceptible and only two isolates tested for tigecycline and one for ertapenem were resistant to those agents. Plasmid-mediated AmpC β -lactamases were identified in one MDR *E. coli* and one *Klebsiella* spp [1/55 and 1/13, respectively]. No carbapenemase-producing Enterobacteriaceae were observed. All MDR *Pseudomonas aeruginosa* strains were extensively drug-resistant (n=8) and half of them were susceptible only to colistin [4/8 (50%)]. None of the included isolates were *Acinetobacter* spp.

With respect to gram-positive microorganisms, *S. aureus* was the most frequent isolate, with MRSA accounting for 16/24 (66.6%). Of the MRSA studied, 12 (75%) were

resistant to fluoroquinolones, 10 (62.5%) to aminoglycosides, 6 (35.7%) to erythromycin, 3 (18.8%) to clindamycin and 2 (12.5%) to tetracycline. All the isolates were susceptible to rifampicin, trimethoprim-sulfamethoxazole, vancomycin, teicoplanin, linezolid and daptomycin.

Epidemiological and clinical features

The baseline characteristics of the patients are described in Table 1. Almost 60% of patients included in the two groups were male. Among MDR isolates, 59/97 (60.8%) were CO-HCA infection. The most frequent risk factors for having a CO-HCA infection were: hospitalization (46/97, 47.4%) in the preceding 90 days, and receipt of chemotherapy, home intravenous therapy or wound care (7/97, 7.2%) in the previous 30 days.

Patients with MDR infections were slightly older than those with non-MDR infections, although the differences were not statistically significant (median age, 77 [IQR 64 to 83.5] vs. 71 [IQR 52 to 82.5], $p=0.129$). When compared against patients with non-MDR microorganisms, patients with MDR infections were significantly more likely to have a higher Charlson Index score (median points, 2 [IQR 1 to 4] vs 2 [IQR 0 to 3]; $p=0.049$), chronic kidney disease (21.6% vs 4.1%; $p<0.001$), prior hospital stay (47.4 vs 21.6%; $p<0.001$), prior antibiotic exposure (36.5% vs 22.7%; $p=0.036$) and prior use of invasive devices (41.2% vs 25.8%; $p=0.023$) in the preceding 3 months.

With respect to source of infection, the most frequently observed site of infection was the urinary tract (UTI) ($n=120$, 61.8%), followed by pneumonia ($n=33$, 17%) and soft skin tissue infections ($n=26$, 13.4%). In both groups, almost 30% of patients included had bloodstream infections (except for one catheter-related bacteremia, all were secondary bacteremia).

Patients with MDR infections were more severely ill at the onset of infection, as shown by higher SOFA scores (median points, 2 [IQR 0 to 3] vs 1 [IQR 0 to 2]; $p<0.001$), a higher rate of patients with septic shock and/or severe sepsis (12.4% vs 4.1%, $p=0.037$) and Pitt score ≥ 2 (25.8% vs 13.4%; $p=0.030$). Patients with MDR infections were also more likely than those with non-MDR infection to receive both inappropriate empirical antibiotic treatment (37.2% vs 6.2%, $p<0.001$) and delayed adequate antibiotic treatment (median days, 2 [IQR 1 to 4] vs 2 [IQR 0 to 4]; $p=0.054$).

Clinical outcome

Clinical failure at day 30 (16.5% vs 7.2%, $p=0.046$) and 1-year all-cause mortality (35.1% vs 21.6%, $p=0.038$) were more frequently observed in patients with MDR infections versus those in the non-MDR group. In addition, MDR cases presented more antibiotic side effects (9.3% vs 1%, $p=0.009$) (Table 1).

Table 2 shows the univariate and multivariate analyses of variables involved in clinical failure at day 30. Age (OR, 1.07; 95% CI, 1.01 to 1.14; $p=0.038$) and SOFA score (OR, 1.45; CI 95%, 1.15 to 1.84; $p=0.002$) were statistically significantly associated with clinical failure in multivariate analysis. Although MDR infection was related to clinical failure in univariate analysis (OR, 2.57; 95% CI, 1.01 to 6.56; $p=0.043$), the association was not statistically significant in multivariate analysis (OR, 0.87, 95% CI, 0.23 to 3.17; $p=0.886$). Cox model regressions of 90-day and 1-year all-cause mortality and 1-year Kaplan-Meier survival curve are shown in Tables S1 and S2 and Figure S1 in the supplementary material. In the multivariate regression model of 90-day all-cause mortality, age (HR, 1.09, 95% CI, 1.03 to 1.16; $p=0.003$) was the only factor associated with poor outcome at day 90. For all-cause mortality at 1 year, aged patients (HR 1.06, 95% CI, 1.03 to 1.09; $p<0.001$) and those with a higher Charlson Index score (HR 1.2, 95% CI, 1.07 to 1.34; $p=0.002$) were more likely to die during the one-year follow-up.

Health care resource consumption and costs

Patients with MDR infection had longer length of hospital stay (median days, 11 [IQR 7 to 16] vs 7 [5 to 11]; $p<0.001$) and stays in the emergency room before hospital admission (median days, 1 [IQR 1 to 2] vs 1 [1 to 1.75]; $p<0.001$) compared with the non-MDR group. No differences in consumption of other resources were observed (Table 3). With respect to cost variables, the overall cost of hospitalization of MDR infections was almost twice the cost associated with the non-MDR bacteria group, with a median difference between the two groups of 2,528 euros ($p<0.001$). Pharmacy and antibiotic treatment costs were also significantly higher in the MDR group (Table 3).

Univariate and multivariate analyses of economic costs per hospital stay and per antibiotic treatment are shown in Table 4. In multivariate analysis, higher Charlson Index (DM 370.79, 95% CI, 92.62 to 648.95 euros; $p=0.009$) and SOFA scores (DM 460.72, 95% CI, 149.2 to 772.25 euros; $p=0.004$) were factors significantly associated with higher overall cost of hospitalization. MDR by itself was not related to increased total costs of hospitalization. In terms of antibiotic costs, however, MDR infection was the only variable associated with higher costs (DM 122.74, 95% CI, 64.75 to 180.73 euros; $p<0.001$).

Discussion

Multiple reports have drawn attention to the worldwide increase in MDR infections over the past decade¹⁻⁴. Whereas multidrug resistance has traditionally been associated with hospital-acquired infection, there has been a worrying increase in community-onset MDR infections in recent years^{7-9,11,12,14}. Several studies have evaluated the clinical and economic impact of hospital-acquired MDR infections¹⁵⁻¹⁷, but little is known about the detrimental effect of MDR bacteria on patients not hospitalized at the

onset of infection. This case-control study evaluated the impact of antimicrobial resistance on clinical and economic outcomes of patients with community-onset MDR infections requiring hospitalization. To our knowledge this is the first study to describe both the clinical and economic consequences of gram-negative and gram-positive MDR infections focusing only on community-onset infections.

We found that the most frequent microorganisms involved in CA and CO-HCA MDR infections were ESBL-producing Enterobacteriaceae and MRSA, which is in line with the high prevalence rates reported in Europe, especially in countries in Southern and Eastern Europe¹³. In addition, at least 40% of included MDR infections were strictly community-acquired. A similar data was observed in a previous Spanish study focused on ESBL *E. coli* UTI requiring hospitalization¹¹. *Rodríguez-Baño et. al* found even higher rates in a multicenter case-control study in which more than 60% of community-acquired ESBL-producing *E. coli* infections were not healthcare-associated⁹. Another study focused on bloodstream infections showed that the percentage of MDR microorganisms was about 20% in Australia³¹. Furthermore, since there was a high rate of resistance among MDR gram-negative isolates in our study to empirical first-line antibiotics, which could lead to higher rates of inappropriate empirical treatment and broad-spectrum antibiotic use, a more accurate strategy is needed to identify patients at risk of community-acquired MDR infection, apart from traditional risk factors³⁰.

The clinical failure rate at day 30 was significantly higher in the MDR group, although our results suggest that this finding was not strictly related to multidrug resistance, but to the fact that elderly patients and higher SOFA scores were more frequently observed in patients with MDR infections. These or equivalent variables have also been previously associated with poor outcomes in community-onset MDR infections^{10,23,31,32}. Whereas patients with MDR infections were less likely to receive appropriate empirical antibiotic treatment, it did not translate into higher clinical failure after adjusting for confounding variables, unlike previous reports^{5,19,33,34}, which were

mainly focused on bacteremia or patients with sepsis where time is a critical factor. In this respect, although nearly 30% of included patients in both groups were bacteremic, only a small proportion of patients in our study had severe sepsis or septic shock or needed to be admitted to intensive care due to infection.

Multidrug resistance was not found to be independently associated with mortality, in accordance with previous studies^{5,10,18,22,23,31,35}. However, other authors have identified antimicrobial resistance as independent predictor of mortality^{19–21,32}. We thought that these conflicting results might be partly influenced by other factors on outcomes apart from multidrug resistance, such as prior conditions, infection severity, source of infection or appropriateness of antibiotic treatment. It has been also hypothesized that acquisition of MDR mechanisms could imply a fitness cost resulting in lower-virulence strains³⁶. Furthermore, it also seems that susceptible strains could trigger a greater host inflammatory response compared to MDR isolates, which could lead to greater severity of infection and poor outcomes³⁷.

In our study, the inclusion of different MDR pathogens could be an additional factor to be highlighted. Due to the local epidemiology, most included isolates were ESBL-producing Enterobacteriaceae and MRSA since carbapenem-producing bacteria or *Acinetobacter* spp. were practically nonexistent in community-onset infections during the study period in our institution. However, carbapenem-producing bacteria or *Acinetobacter* spp. are classically associated with worse outcomes^{4,38,39} and classified as critical on the World Health Organization priority pathogens list⁴⁰. Thus, our results might be not necessarily transferable to other settings with a different epidemiology.

With respect to long-term mortality, although according to the Kaplan-Meier curves, patients with MDR infections were more likely to die at 1-year follow-up, only age and Charlson Index were independently associated with mortality. It is worthy of note that mean age was particularly high in our study, mainly in the MDR group, and almost half the included patients also had an elevated Charlson Index score (≥ 3 points). As

Vardakas et al. suggested¹, it may be difficult to determine whether outcomes in MDR infection are more influenced by patients' underlying diseases than by multidrug resistance as such. Consequently, multidrug resistance seems to be the tip of the iceberg, warning of a more complex, vulnerable patient.

As previous studies, MDR infections presented longer length of stay^{3,15–19,21,22,41,42} and higher antibiotic treatment costs^{19,21,22}. In addition, the overall hospitalization costs of MDR infections were almost twice those for the non-MDR group. Nevertheless, this was not strictly related to multidrug resistance, but rather to the higher frequency of older patients and a greater proportion of severe infections in the MDR group. This finding comes as a surprise, since antimicrobial resistance has traditionally been associated with higher costs^{3,15,17–19,21,22,41–43}. In contrast to our study, in which we only addressed community-onset infections, many previous studies have included hospital-acquired MDR infections^{15,17,41–43}, hence costs may have been overestimated because they considered total hospitalization costs. In addition, some of these studies did not adjust for confounders, so they might have overlooked the burden of other factors^{19,22,41}. In our study, for instance, in the univariate analysis the overall hospitalization costs of MDR infections almost doubled those for the non-MDR group. Another explanation to justify this unexpected finding could be the type of MDR included. A study carried out in Viena showed that hospital costs of patients with MDR gram-negative microorganisms were greater compared to the costs of patients with MRSA⁴⁴. In line with this, other studies have not found differences in total hospital cost in patients with MRSA versus oxacillin-susceptible community-acquired isolates³⁵. On the contrary, in case of ESBL- or carbapenem-producing bacteria most of studies have identified higher hospital costs compared with ESBL- or carbapenem-negative strains^{15,17–19,21,41,43}. Therefore, the type of the microorganisms included in our study, with more than 15% of MRSA and no carbapenem-producing bacteria or *Acinetobacter* spp. in the MDR group; the inclusion of exclusively community-onset MDR infections,

and the lack of adjustment for confounders in some previous studies could be among the reasons of these results.

Setting aside the economic cost itself, MDR infections are known to be closely linked to greater consumption of healthcare resources^{2,3}. In our study, for instance, there were few or even no opportunities to use oral antibiotic treatment for many of the MDR isolates, which could lead to hospital admission or outpatient parenteral antibiotic therapy, both of which could be avoided with an antimicrobial-susceptible isolation. Further, MDR infections can interfere with normal hospital activity because of the need for special environmental cleanup measures, isolation rooms and consumables (masks, gloves, gowns, etc.), with loss of hospital beds or delayed discharge to long-term care centers because a private room is necessary. Furthermore, patients in isolation rooms can be prone to worse functional recovery, which could translate into the need for rehabilitation and longer hospital stay. From the point of view of resource management of healthcare systems, MDR infections seems to be an indicator of a more complex and expensive admission process compared to non-MDR infections, whether because of greater clinical severity, underlying diseases, length of stay or other special measures.

This study has certain limitations. First, all clinical data were obtained retrospectively, and are therefore more vulnerable to possible bias. Second, the small sample size and single hospital site may not represent all community-onset MDR infections. Third, although an attempt was made to match for infection site and microorganism, not all included patients were matched on both criteria, although no statistical differences in these characteristics were observed between groups. Fourth, a heterogeneous sample of microorganisms was included and analyzed as a whole. This might potentially overlook the impact of individual bacteria on prognosis and healthcare costs, although this was not part of our purpose. Lastly, other outcomes of interest that might provide a broader picture of the impact of multidrug resistance, such as quality of life, the

psychological impact of MDR infections and social resource consumption, the economic impact of occupancy of double rooms as single isolation rooms, were not assessed. On the other hand, a series of strengths of this study can be highlighted. Only patients for whom infection was the reason for admission were included, which eliminates the biases of many studies in which included patients have longer hospital stays before the infection episode, which overestimates the impact of these costs primarily in patients with infections caused by MDR microorganisms. On the other hand, the fact of including MDR strains of different microorganisms reflects the current clinical reality of many acute care hospitals.

In conclusion, this study identified worse clinical and economic outcomes in patients admitted as a result of community-onset MDR infections. Although worse outcomes were not strictly related to multidrug resistance as such, but to greater clinical severity and underlying diseases, multidrug resistance was associated with longer hospital stays and higher antibiotic costs. Consequently, the admission process associated with patients with community-onset MDR bacterial infections is more complex and expensive than for patients with similar non-MDR infections. This should be acknowledged by healthcare managers in order to improve healthcare processes and invest more in the prevention and control of antibiotic resistance.

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Declaration of interest

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References

- 1 Vardakas Konstantinos Z., Rafailidis Petros I., Konstantelias Athanasios A., Falagas Matthew E. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: The study, the patient, the bug or the drug? *J Infect* 2013;**66**(5):401–14. Doi: 10.1016/j.jinf.2012.10.028.
- 2 Friedman N. D., Temkin E., Carmeli Y. The negative impact of antibiotic resistance. *Clin Microbiol Infect* 2016;**22**(5):416–22. Doi: 10.1016/j.cmi.2015.12.002.
- 3 Cosgrove Sara E. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006;**42**(Suppl 2):S82–9. Doi: 10.1086/499406.
- 4 Cassini Alessandro, Högberg Liselotte Diaz, Plachouras Diamantis, Quattrocchi Annalisa, Hoxha Ana, Simonsen Gunnar Skov, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;**19**(1):56–66. Doi: 10.1016/S1473-3099(18)30605-4.
- 5 Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Ruíz M, Peña C, Almela M, Almirante B, Grill F, Colomina J, Giménez M, Oliver A, Horcajada JP, Navarro G, Coloma A Pascual A; Spanish Network for Research in Infectious Diseases (REIPI). Community-Onset Bacteremia Due to Extended- Spectrum β -Lactamase – Producing *Escherichia coli*: Risk Factors and Prognosis. *Clin Infect Dis* 2010;**50**(1):40–8. Doi: 10.1086/649537.
- 6 Cecchini Michele, Langer Julia, Slawomirski Luke. Resistance in G7 countries and beyond: economic issues, policies. *Paris Organ Econ Co-Operation Dev* 2015;(September).

- 7 Van Duin David, Paterson David. Multidrug Resistant Bacteria in the Community: Trends and Lessons Learned. *Infect Dis Clin North Am* 2017;**30**(2):377–90. Doi: 10.1016/j.idc.2016.02.004.Multidrug.
- 8 Wolfe Caitlin M., Cohen Bevin, Larson Elaine. Prevalence and risk factors for antibiotic-resistant community-associated bloodstream infections. *J Infect Public Health* 2014;**7**(3):224–32. Doi: 10.1016/j.jiph.2014.01.001.
- 9 Rodríguez-Baño Jesús, Alcalá Juan C., Cisneros Jose M., Grill Fabio, Oliver Antonio, Horcajada Juan P., et al. Community Infections Caused by Extended-Spectrum β -Lactamase–Producing *Escherichia coli*. *Arch Intern Med* 2008;**168**(17):1897. Doi: 10.1001/archinte.168.17.1897.
- 10 Park Sun Hee, Choi Su Mi, Lee Dong Gun, Kim Jayoung, Choi Jung Hyun, Kim Si Hyun, et al. Emergence of extended-spectrum β -lactamase-producing *Escherichia coli* as a cause of community-onset bacteremia in south korea: Risk factors and clinical outcomes. *Microb Drug Resist* 2011;**17**(4):537–44. Doi: 10.1089/mdr.2011.0072.
- 11 Ángel Díaz Miguel, Ramón Hernández José, Martínez-Martínez Luis, Rodríguez-Baño Jesús, Pascual Álvaro, Martínez Peinado Carmen, et al. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Spanish hospitals: 2nd multicenter study (GEIH-BLEE project, 2006). *Enferm Infecc Microbiol Clin* 2009;**27**(9):503–10. Doi: 10.1016/j.eimc.2008.09.006.
- 12 DeLeo Frank R, Otto Michael, Kreiswirth Barry N, Chambers Henry F. Community-associated methicillin-resistant *Staphylococcus aureus*. *Lancet* 2010;**375**(9725):1557–68. Doi: 10.1016/S0140-6736(09)61999-1.
- 13 *European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial*

- Resistance Surveillance Network (EARS-Net) 2017. Stockholm: ECDC; 2018.*
- 2017.
- 14 Kelly Ana M., Mathema Barun, Larson Elaine L. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. *Int J Antimicrob Agents* 2017;**50**(2):127–34. Doi: 10.1016/j.ijantimicag.2017.03.012.
 - 15 Thaden Joshua T., Li Yanhong, Ruffin Felicia, Maskarinec Stacey A., Hill-Rorie Jonathan M., Wanda Lisa C., et al. Increased costs associated with bloodstream infections caused by multidrug-resistant gram-negative bacteria are due primarily to patients with hospital-acquired infections. *Antimicrob Agents Chemother* 2017;**61**(3):1–10. Doi: 10.1128/AAC.01709-16.
 - 16 Lye D C, Earnest A, Ling M L, Lee T, Yong H, Fisher D A, et al. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay : cohort study. *Clin Microbiol Infect* 2011;**18**(5):502–8. Doi: 10.1111/j.1469-0691.2011.03606.x.
 - 17 Huang Wenzhi, Qiao Fu, Zhang Yinying, Huang Jing, Deng Yuhua, Li Jinwen, et al. In-hospital Medical Costs of Infections Caused by Carbapenem-resistant *Klebsiella pneumoniae*. *Clin Infect Dis* 2018;**67**(suppl_2):S225–30. Doi: 10.1093/cid/ciy642.
 - 18 Esteve-Palau E., Solande G., Sánchez F., Sorlí L., Montero M., Güerri R., et al. Clinical and economic impact of urinary tract infections caused by ESBL-producing *Escherichia coli* requiring hospitalization: A matched cohort study. *J Infect* 2015;**71**(6):667–74. Doi: 10.1016/j.jinf.2015.08.012.
 - 19 Apisarnthanarak Anucha, Kiratisin Pattarachai, Mundy Linda M. Predictors of Mortality From Community-Onset Bloodstream Infections Due to Extended-Spectrum β -Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol* 2008;**29**(7):671–4. Doi: 10.1086/588082.

- 20 Apisarnthanarak Anucha, Kiratisin Patarachai, Saifon Piyawan, Kitphati Rungrueng, Dejsirilert Surang, Mundy Linda M. Predictors of Mortality Among Patients With Community-Onset Infection Due to Extended-Spectrum β -Lactamase-Producing *Escherichia coli* in Thailand. *Infect Control Hosp Epidemiol* 2008;**29**(1):80–2. Doi: 10.1086/524321.
- 21 Hu Bijie, Ye Huifeng, Xu Yingchun, Ni Yuxing, Hu Yunjian, Yu Yunsong, et al. Clinical and economic outcomes associated with community-acquired intra-abdominal infections caused by extended spectrum beta-lactamase (ESBL) producing bacteria in China. *Curr Med Res Opin* 2010;**26**(6):1443–9. Doi: 10.1185/03007991003769068.
- 22 MacVane Shawn H., Tuttle Lindsay O., Nicolau David P. Impact of extended-spectrum β -lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *J Hosp Med* 2014;**9**(4):232–8. Doi: 10.1002/jhm.2157.
- 23 Wang J.-L., Chen S.-Y., Wang J.-T., Wu G. H.-M., Chiang W.-C., Hsueh P.-R., et al. Comparison of Both Clinical Features and Mortality Risk Associated with Bacteremia due to Community-Acquired Methicillin-Resistant *Staphylococcus aureus* and Methicillin-Susceptible *S. aureus*. *Clin Infect Dis* 2008;**46**(6):799–806. Doi: 10.1086/527389.
- 24 Magiorakos A. P., Srinivasan A., Carey R. B., Carmeli Y., Falagas M. E., Giske C. G., et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;**18**(3):268–81. Doi: 10.1111/j.1469-0691.2011.03570.x.
- 25 Charlson Mary E, Pompei Peter, Ales Kathy L, MacKenzie Ronald C. A New Method of Classifying Prognostic in Longitudinal Studies: Development. *J*

- Chronic Dis* 1987;**40**(5):373–83. Doi: 10.1016/0021-9681(87)90171-8.
- 26 Singer Mervyn, Deutschman Clifford S., Seymour Christopherwarren, Shankar-Hari Manu, Annane Djillali, Bauer Michael, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA - J Am Med Assoc* 2016;**315**(8):801–10. Doi: 10.1001/jama.2016.0287.
 - 27 Jones AE, Trzeciak S Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med* 2010;**37**(5):1649–54. Doi: 10.1097/CCM.0b013e31819def97.
 - 28 Rhee Ji Young, Kwon Ki Tae, Ki Hyun Kyun, Shin Sang Yop, Jung Dong Sik, Chung Doo Ryeon, et al. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: A comparison of the PITT bacteremia score and the acute physiology and chronic health evaluation II scoring systems. *Shock* 2009;**31**(2):146–50. Doi: 10.1097/SHK.0b013e318182f98f.
 - 29 Definitions Surveillance. CDC / NHSN Surveillance Definitions for Specific Types of Infections 2018;(January):1–30.
 - 30 Friedman N Deborah, Kaye Keith S, Stout Jason E, McGarry Sarah A, Trivette Sharon L, Briggs Jane P, et al. Health Care–Associated Bloodstream Infections in Adults: A Reason To Change the Accepted Definition of Community-Acquired Infections. *Ann Intern Med* 2002;**137**(10):791–7. Doi: 10.7326/0003-4819-137-10-200211190-00007.
 - 31 Lim Ching J., Cheng Allen C., Kong David C.M., Peleg Anton Y. Community-onset bloodstream infection with multidrug-resistant organisms: A matched case-control study. *BMC Infect Dis* 2014;**14**(1):1–9. Doi: 10.1186/1471-2334-14-126.
 - 32 Kang Cheol-In, Song Jae-Hoon, Chung Doo Ryeon, Peck Kyong Ran, Ko Kwan

- Soo, Yeom Joon-Sup, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum β -lactamase-producing *Escherichia coli*. *Int J Antimicrob Agents* 2010;**36**(3):284–7. Doi: 10.1016/j.ijantimicag.2010.05.009.
- 33 Valle Jordi. Community-Acquired Bloodstream Infection in Critically Ill Adult Patients: Impact of Shock and Inappropriate Antibiotic Therapy on Survival 2003:1615–24. Doi: 10.1378/chest.123.5.1615.
- 34 Paul Mical, Shani Vered, Muchtar Eli, Kariv Galia, Robenshtok Eyal, Leibovici Leonard, et al. Systematic Review and Meta-Analysis of the Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis 2010;**54**(11):4851–63. Doi: 10.1128/AAC.00627-10.
- 35 Taneja Charu, Haque Nadia, Oster Gerry, Shorr Andrew F., Zilber Sophia, Kyan Paola Osaki, et al. Clinical and economic outcomes in patients with community-acquired *Staphylococcus aureus* pneumonia. *J Hosp Med* 2010;**5**(9):528–34. Doi: 10.1002/jhm.704.
- 36 Andersson Dan I, Hughes Diarmaid. Antibiotic resistance and its cost: is it possible to reverse resistance? *Nat Publ Gr* 2010;**8**(4):260–71. Doi: 10.1038/nrmicro2319.
- 37 Gómez-zorrilla Silvia, Calatayud Laura, Juan Carlos, Cabot Gabriel, Tubau Fe, Oliver Antonio, et al. Understanding the acute inflammatory response to *Pseudomonas aeruginosa* infection: differences between susceptible and multidrug-resistant strains in a mouse peritonitis model. *Int J Antimicrob Agents* 2016. Doi: 10.1016/j.ijantimicag.2016.10.016.
- 38 Falagas Matthew E, Tansarli Giannoula S, Karageorgopoulos Drosos E, Vardakas Konstantinos Z. Deaths Attributable to Carbapenem-Resistant Enterobacteriaceae Infections. *Emerg Infect Dis* 2014;**20**(7):1170–5. Doi:

10.3201/eid2007.121004.

- 39 Russo Alessandro, Bassetti Matteo, Ceccarelli Giancarlo, Carannante Novella, Losito Angela Raffaella, Bartoletti Michele, et al. Bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*: Clinical features, therapy and outcome from a multicenter study. *J Infect* 2019;**79**(2):130–8. Doi: 10.1016/j.jinf.2019.05.017.
- 40 WHO. WHO publishes list of bacteria for which new antibiotics are urgently needed. Media Centre. News Release. 2017.
- 41 Maslikowska J. A., Walker S. A.N., Elligsen M., Mittmann N., Palmay L., Daneman N., et al. Impact of infection with extended-spectrum β -lactamase-producing *Escherichia coli* or *Klebsiella* species on outcome and hospitalization costs. *J Hosp Infect* 2016;**92**(1):33–41. Doi: 10.1016/j.jhin.2015.10.001.
- 42 Neidell Matthew J., Cohen Bevin, Furuya Yoko, Hill Jennifer, Jeon Christie Y., Glied Sherry, et al. Costs of Healthcare- and Community-Associated Infections With Antimicrobial-Resistant Versus Antimicrobial-Susceptible Organisms. *Clin Infect Dis* 2012;**55**(6):807–15. Doi: 10.1093/cid/cis552.
- 43 Zhen X., Chen Y., Hu X., Dong P., Gu S., Sheng Y. Y., et al. The difference in medical costs between carbapenem-resistant *Acinetobacter baumannii* and non-resistant groups: a case study from a hospital in Zhejiang province, China. *Eur J Clin Microbiol Infect Dis* 2017;**36**(10):1989–94. Doi: 10.1007/s10096-017-3088-3.
- 44 Daxboeck F, Budic T, Assadian O, Reich M, Koller W. Economic burden associated with multi-resistant Gram-negative organisms compared with that for methicillin-resistant *Staphylococcus aureus* in a university teaching hospital. *J Hosp Infect* 2006;**62**(2):214–8. Doi: 10.1016/j.jhin.2005.07.009.

Table 1. Univariate analysis of patient characteristics for non-MDR (controls) and MDR (cases) infections.

Table 2. Univariate and multivariate analyses of factors related to clinical failure at day 30.

Table 3. Univariate analyses of healthcare resource consumption and economic impact of non-MDR (controls) and MDR (cases) infections.

Table 4. Univariate and multivariate analyses of economic costs per overall hospital stay and antibiotic treatment.

Figure 1. Proportion of MDR organisms versus non-MDR organisms in study patients.

Tables

Table 1. Univariate analysis of patient characteristics for non-MDR (controls) and MDR (cases) infections.

Clinical variable	Controls (n=97)	Cases (n=97)	p-value
Age, m (IQR), y	71 (52-82.5)	77 (64-83.5)	0.129
Male sex	57 (58.8)	58 (59.8)	0.884
HCA risk factors			
Hospital stay last 3mo	21 (21.6)	46 (47.4)	<0.001
Residence in long-term care facility	1 (1)	4 (4.1)	0.368
Chemotherapy, home intravenous therapy or wound care in last 30d	5 (5.2)	7 (7.2)	0.551
Dialysis in last 30d	1 (1)	3 (3.1)	0.621
Antibiotic exposure in last 3mo	22 (22.7)	35 (36.5)	0.036
Invasive devices in last 3mo	25 (25.8)	40 (41.2)	0.023
Indwelling catheter	16 (16.5)	25 (25.8)	0.113
Vascular access	19 (19.6)	26 (26.8)	0.234
Absence of comorbidity	40 (41.2)	32 (33)	0.234
Charlson Index, m (IQR)	2 (0-3)	2 (1-4)	0.049
Charlson Index ≥ 3	39 (40.2)	47 (48.5)	0.258
Cardiovascular disease	23 (23.7)	23 (23.7)	1
Peripheral vascular disease	16 (16.5)	13 (13.4)	0.546
Cerebrovascular disease	10 (10.3)	16 (16.5)	0.206
Dementia	9 (9.5)	15 (15.5)	0.191
COPD	26 (26.8)	27 (27.8)	0.872
Diabetes	27 (27.8)	31 (32)	0.530
Renal disease	4 (4.1)	21 (21.6)	<0.001
Malignancy	24 (24.7)	19 (19.6)	0.387
Immunosuppression	2 (2.1)	6 (6.2)	0.279
Site of infection			
Pneumonia	19 (19.3)	14 (14.4)	0.339
UTI	55 (56.7)	65 (67)	0.139
SSTI	15 (15.5)	11 (11.3)	0.339
IAI	8 (8.2)	4 (4.1)	0.233
Other	0 (0)	3 (3.1)	0.246
Bacteremia	28 (28.6)	29 (29.9)	0.875
Severity of infection			
SOFA, m (IQR)	1 (0-2)	2 (0-3)	<0.001

Septic shock and/or severe sepsis	4 (4.1)	12 (12.4)	0.037
Pitt Score, m (IQR)	0 (0-1)	(0-2)	0.077
Pitt Score ≥ 2	13 (13.4)	25 (25.8)	0.030
ICU stay (first 72h)	4 (4.1)	3 (3.1)	1.000
Need for surgery	15 (15.5)	16 (16.5)	0.845
Management			
Appropriate empiric treatment	90 (93.8)	59 (62.8)	<0.001
Appropriate definitive treatment	94 (98.9)	92 (94.8)	1.000
Time to adequate antibiotic treatment, m (IQR), d	2 (0-4)	2 (1-4)	0.054
72h delay to start appropriate antibiotic treatment ^a	36 (39.6)	45 (48.9)	0.203
Days of antibiotics, m (IQR), d	13 (10-15.5)	13.5 (11-16)	0.584
Antibiotic side effects	1(1)	9 (9.3)	0.009
Outcomes			
Clinical failure day 30	7 (7.2)	16 (16.5)	0.046
All-cause mortality			
90-day	8 (8.2)	16 (16.5)	0.081
1-year	21 (21.6)	34 (35.1)	0.038

Data are presented as n (%), unless otherwise specified. Abbreviations: m (median), IQR (interquartile range), MDR (multidrug-resistant), HCA (healthcare-associated), COPD (Chronic Obstructive Pulmonary Disease), UTI (Urinary Tract Infection), SSTI (Soft Skin Tissue Infection), IAI (Intraabdominal Infection), SOFA (Sequential Organ Failure Assessment), ICU (Intensive Care Unit), h (hours), d (days), mo (months), y (year).

^a 72h delay to start antibiotic appropriate treatment refers to a delay of at least 72 hours to start of appropriate empiric or definitive treatment following a positive culture.

Table 2. Univariate and multivariate analyses of factors related to clinical failure at day 30

Clinical variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	aOR (95%CI)	p-value
Age	1.03 (1.01-1.06)	0.050	1.07 (1.01-1.14)	0.038
Charlson Index	1.19 (0.98-1.43)	0.066	1.04 (0.76-1.41)	0.807
Hospital stay last 3mo	0.81 (0.32-2.08)	0.816		
Antibiotic exposure last 3mo	0.2 (0.04-0.88)	0.026		
Invasive devices last 3mo	0.51 (0.18-1.45)	0.203		
MDR infection	2.57 (1.01-6.56)	0.043	0.87 (0.23-3.17)	0.886
UTI	0.95 (0.39-2.33)	0.917		
Pneumonia	2.44 (0.91-6.51)	0.079	1.99 (0.54-7.4)	0.300
SSTI	0.27 (0.3-2.06)	0.324		
IAI	0.66 (0.8-5.37)	1		
Bacteremia	2.03 (0.83-4.94)	0.114		
Pitt Score	1.48 (1.01-2.17)	0.042	1.25 (0.77-2.04)	0.366
SOFA Score	1.48 (1.22-1.79)	<0.001	1.45 (1.15-1.84)	0.002
Septic shock and/or severe sepsis	1.83 (0.48-6.99)	0.368		
ICU stay (first 72h)	1.25 (0.14-10.87)	0.593		
Need for surgery	0.77 (0.21-2.75)	1		
Appropriate empirical treatment	0.92 (0.32-2.66)	0.878		
Appropriate definitive treatment	0.12 (0.01-2.01)	0.211		
72h delay to appropriate treatment	1.28 (0.51-3.24)	0.604		

Abbreviations: OR (Odds ratio), aOR (adjusted odds ratio), CI (Confidence Interval), MDR (multidrug-resistant), UTI (urinary tract infection), SSTI (soft skin tissue infection), IAI (Intraabdominal Infection), SOFA (Sequential Organ Failure Assessment), ICU (intensive care unit), h (hours), mo (months).

Table 3. Univariate analysis of health care resource consumption and economic impact of non-MDR (controls) and MDR (cases) infections.

	Controls	Cases	p-value
Healthcare resource consumption			
Length of stay, d	7 (5-11)	11 (7-16)	<0.001
Length of stay in emergency room, d	1 (1-1,75)	1 (1-2)	<0.001
Need for OPAT, n (%)	3 (3.1)	6 (6.2)	0.306
Outpatient visits, 3mo	1 (0-3)	0 (0-3)	0.252
Outpatient visits related to infection, 3mo, n (%)	24 (24.7)	19 (19.6)	0.387
Readmissions, 1y	0 (0-1)	1 (0-2)	0.137
Readmissions related to infection, 1y, n (%)	16 (16.5)	27 (27.8)	0.057
Costs, €			
Overall cost of hospitalization	2659 (1743-5020)	5187 (2818-8364)	<0.001
Cost of pharmacy	48 (19-108)	250 (51-477)	<0.001
Cost of antibiotic treatment	12 (4-36)	148 (22-338)	<0.001
Cost of laboratory tests	119 (50-228)	143 (63-306)	0.228
Cost of imaging plus other complementary tests	28 (7-109)	39 (7-200)	0.183

Data are presented as mean (m) and interquartile range (IQR) unless otherwise specified. Cost values are presented in Euros (€). Abbreviations: MDR (multidrug-resistant), OPAT (outpatient parenteral antibiotic therapy), d (days), mo (months), y (year).

Table 4. Univariate and multivariate analysis of economic costs of overall hospital stay and antibiotic treatment.

	DM (95%CI)	p-value	Adjusted DM (95%CI)	p-value
Overall cost of hospitalization				
Age	22.05 (-12.98-57.01)	0.216		
Charlson Index	397.03 (124.52-669.53)	0.002	370.79 (92.62-648.95)	0.009
MDR infection	2527 (1549.61-3505.94)	<0.001	976.87 (-325.27-2279.01)	0.140
SOFA Score	690.07 (623.34-1296.81)	<0.001	460.72 (149.2-772.25)	0.004
Severe sepsis and/or septic shock	2744.88 (520.79-4968.97)	0.016	1330.61 (-1257.05-3918.27)	0.311
Appropriate empiric treatment	-2127.09 (-3527.51- -726.67)	0.003	-1048.23 (-2580.74-484.27)	0.178
72h delay to treatment	1285.66 (200.64-2370.68)	0.02	800.81 (-354.91-1956.54)	0.173
Cost of antibiotic treatment				
Age	0.73 (0.49-1.96)	0.244		
Charlson Index	11.65 (1.62-21.68)	0.023	3.42 (-9.3-16.14)	0.596
MDR infection	137.9 (89.94-185.87)	<0.001	122.74 (64.75-180.73)	<0.001
SOFA Score	18.39 (5.95-30.83)	0.004	5.08 (-8.19-18.35)	0.450
Severe sepsis and/or septic shock	42.6 (-27.27-110.47)	0.217		
Appropriate empiric treatment	-123.37 (-163.16-83.58)	<0.001	-34.62 (-101.68-32.46)	0.309
72h delay to treatment	24.26 (-16.99-65.51)	0.247		

Values are presented in Euros. Abbreviations: DM (difference of medians), CI (confidence Interval), MDR (multidrug resistance), SOFA (sequential organ failure assessment), h (hours).

Figures

Figure 1. Proportions of MDR versus non-MDR organisms in study patients.

“Others” in the non-MDR-group refers to: *Haemophilus influenzae* (n=8, 6/8 beta-lactamase-negative), *viridans* group streptococci (n=6), *Streptococcus pneumoniae* (n=2, Serotype 7C and 14, non-penicillin-resistant) and one isolate each of *Enterococcus faecalis*, *Morganella morganii* and *Providencia* spp.; and in MDR group to *Providencia* spp (n=2) and one isolate each of *Enterobacter cloacae* and *Staphylococcus epidermidis*.

Abbreviations: MDR (multidrug-resistant).