Relationship between consumption of MRSA-active antibiotics and burden of MRSA in acute care hospitals in Catalonia, Spain

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Objectives: To analyse the possible relationship between consumption of old and new MRSA-active antibiotics and burden of MRSA in acute care hospitals in Catalonia during the period 2007–12.

Methods: Fifty-four hospitals participating in the VINCat Programme were included. Proportion of MRSA (resistant isolates of Staphylococcus aureus per 100 isolates of S. aureus tested), incidence of new cases of infection [new cases of MRSA per 1000 occupied bed-days (OBD)] and incidence of cases of bacteraemia (MRSA bacteraemia cases per 1000 OBD) were determined to estimate the annual MRSA burden. Antibiotic consumption was calculated in DDD/100 OBD. Cost was expressed in euros/100 OBD.

Results: MRSA rates remained stable over the study period, with the proportion of MRSA ranging from 20% to 22.82% in 2007 and 2012, respectively (P = 0.864). Consumption of old MRSA-active antibiotics (vancomycin and teicoplanin) did not change significantly, with values from 1.51 to 2.07 DDD/100 OBD (P = 0.693). Consumption of new MRSA-active antibiotics (linezolid and daptomycin) increased significantly, with values rising from 0.24 to 1.49 DDD/100 OBD (P < 0.001). Cost increased by almost 200%.

Conclusions: A widespread and steady increase in consumption of new MRSA-active antibiotics was observed among acute care hospitals in Catalonia, in spite of a stable MRSA burden. At the same time, consumption of old drugs remained stable. Such trends resulted in a significant increase in cost. Our findings suggest that factors other than the proportion of methicillin resistance among S. aureus may influence the use of old and new MRSA-active antibiotics in the clinical setting.

Keywords: defined daily dose, MRSA, vancomycin, teicoplanin, linezolid, daptomycin

Introduction

Monitoring hospital consumption of antibacterial agents, particularly of novel drugs active against multiresistant microorganisms, constitutes an essential part of antimicrobial stewardship programmes.1,2 Both linezolid and daptomycin are new antibiotics active against MRSA, which have been added to the pre-existing arsenal that includes glycopeptides, such as vancomycin and teicoplanin, as first-line parenteral agents against systemic MRSA infections.3

Although different scenarios can lead to the use of these drugs in hospitalized patients, the most important factor in their overall use should be the local burden of MRSA. To date, few studies have been published correlating rates of MRSA infection with in-hospital consumption of antibiotics active against this microorganism.

The aim of this study was to analyse the possible relationship between the consumption of old and new antibiotics active against MRSA and the rates of MRSA infections in the acute care hospitals of Catalonia, an autonomous community in Spain, during the period 2007–12. We also sought to determine the economic cost associated with the consumption of the different agents.
Methods

Setting and study design

To conduct this retrospective observational study, the in-hospital consumption of antibiotics active against MRSA and the MRSA rates of the participating centres (including proportion of MRSA, annual incidence of new cases of infection and incidence of cases of bacteraemia) were determined and analysed. For the purposes of this study, linezolid and daptomycin were considered the new antibiotics active against MRSA and vancomycin and teicoplanin the old ones. Data were obtained from the VINCat Programme (a standardized surveillance system of hospital-acquired infections in acute care hospitals in Catalonia, Spain) for the period 2007–12. Catalonia is an autonomous community in the north-east of Spain with a population of 7.5 million and has its own unitary health authority. All acute care hospitals that met the pre-established criteria for admission into the VINCat Programme were invited to participate in the study. Specific data management training was imparted in all the participating hospitals before implementation of the programme. The economic cost of antibiotics was obtained from the ‘Catalogue of the General Council of Pharmacists of Spain, 2012’.

Data collection

The VINCat Coordinating Centre was responsible for establishing the criteria for data compilation. Data were collected for the consumption of antibiotics (J01) according to the Anatomical Therapeutic Chemical classification system. The consumption of vancomycin, teicoplanin, linezolid and daptomycin in acute care hospitals was recorded; data were excluded from paediatrics, hospital wards that generated very low consumption (e.g. psychiatry) and those that did not register any occupied bed-days (OBD). Consumption was calculated and expressed in DDD/100 OBD. The 2014 update of DDD was applied (vancomycin, 2 g; teicoplanin, 0.4 g; linezolid, 1.2 g; and daptomycin, 0.28 g). Data from participating hospitals were collected once a year. Hospitals that provided data obtained using non-standardized methods were excluded. All the data were downloaded and processed using a local program designed and built as part of VINCat.

For the calculation of MRSA indicators, all patients treated in any acute care area of the hospitals were included. Cases of MRSA were determined based on antimicrobial susceptibility reports provided by the microbiology laboratory during each period, according to standard procedures. Proportion of MRSA was defined as the proportion of MRSA isolates over the total number of Staphylococcus aureus (number of resistant isolates per 100 isolates tested, only considering one isolate per patient). Samples from active surveillance of carriers were not included. The MRSA incidence was calculated as the number of new cases of MRSA infection per 1000 OBD. The incidence of MRSA bacteraemia was the number of MRSA bacteraemia cases per 1000 OBD. The detailed methodology used is described in a previous VINCat publication.

Statistical analysis

Trends in antibiotic use, resistance and costs were examined using a linear mixed model with the hospital as a cofactor and the year as a covariate. We tested whether the linear mixed regression coefficient was significantly different from zero. P values of <0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Analysis was performed for all hospitals and also after classifying the hospitals by size: >500 beds; between 200 and 500 beds; and <200 beds. Finally, the analysis was repeated for the evolution of the cost of the different antibiotics, expressed in euros/100 OBD.

Results

Data from 54 hospitals participating in the VINCat Programme were analysed. Table 1 shows the proportion of MRSA and incidence rates and trends in the consumption of new and old MRSA-active antibiotics and associated costs over the study period.

Overall MRSA rates (including proportion of MRSA, incidence of new cases of infection and incidence of episodes of bacteraemia) remained stable over the study period, whereas the overall consumption of MRSA-active antibiotics increased significantly. This increase was due to the increased consumption of both linezolid and daptomycin, since the consumption of vancomycin and teicoplanin did not change significantly.

The consumption of vancomycin was always between two and three times higher than that of the other agents, ranging from 1.04 to 1.5 DDD/100 OBD. The consumption of daptomycin overtook that of linezolid in the last 2 years of the study period, reaching a maximum of 0.87 DDD/100 OBD in 2012.

The cost of MRSA-active antibiotics increased by almost 200% over the study period. This increase was mainly due to the increase in consumption of new drugs. In 2007, the first year of the study, the old antibiotics and the new ones represented a similar cost: 28.45 and 27.84 euros/100 OBD, respectively. By 2012, the cost of the old antibiotics had increased to 39.18 euros/100 OBD (P=0.310), while that of the new drugs had clearly undergone a much greater increase, reaching 129.40 euros/100 OBD (P<0.001). Costs attributable to linezolid consumption led the antibiotic expenditure every year whereas costs resulting from the daptomycin consumption showed the most marked upward trend.

The specific analysis of MRSA rates, antibiotic consumption and costs, divided into three groups according to hospital size, did not reveal important differences in the trends observed in the whole population. Detailed data are provided in Tables S1, S2 and S3 (available as Supplementary data at JAC Online). The overall anti-MRSA antibiotic consumption was higher among large hospitals (5.63 DDD/100 OBD in 2012) than among medium-sized (2.36 DDD/100 OBD) and small hospitals (1.75 DDD/100 OBD). Of note, in medium-sized and small hospitals the consumption of linezolid remained higher than that of daptomycin over the entire study period.

Discussion

Our study shows that despite the proportion of MRSA and incidence rates having remained unchanged in recent years in acute care hospitals in Catalonia, the consumption of antibiotics active against this microorganism increased significantly. Similar trends were observed for the whole population and when the analysis was stratified according to hospital size. This widespread situation is mainly the consequence of a steady increase in the consumption of linezolid and daptomycin, coupled with stabilization in the consumption of vancomycin and teicoplanin.

To the best of our knowledge, only one similar study has been reported in the literature, showing an increasing consumption of MRSA-active drugs without increasing MRSA rates in 55 German ICUs over the period 2001–09. In that study, the new drug on the increase was mainly linezolid, administered to critically ill patients with ventilator-associated pneumonia, whereas old drugs stayed stable, indicating that new MRSA-active antibiotics did not replace old ones, but were added on top.

Among others, the major discrepancy between the burden of resistance and antibiotic consumption observed in our study may...
be indicative of the occurrence of the following features: (i) an overestimation of MRSA as the causative agent of infections treated empirically in our hospitals; (ii) an expanded use of the new MRSA-active antibiotics for therapeutic indications that were originally unlicensed but are now being considered in the light of favourable clinical or experimental data, e.g. in the case of MRSA prosthetic joint infections; (iii) the frequent use of doses higher than initially recommended in pivotal clinical trials, which may be especially relevant for daptomycin; (iv) an increased use of the new drugs for treating infections caused by other Gram-positive bacteria, which is an improbable explanation here since infections caused by VRE are extremely rare in our country; and (v) the pressure brought to bear by the pharmaceutical industry, which has been identified as a key element that would explain an important proportion of the increase in prescriptions corresponding to the new drugs.

All things considered, the increase in the consumption of new MRSA-active drugs is not surprising and would be well explained by their pharmacokinetic and pharmacodynamic advantages over vancomycin and by the marginal superiority exhibited in a limited number of clinical trials, especially in the case of linezolid in patients with nosocomial pneumonia caused by MRSA and in the case of daptomycin in patients with bacteraemia.

Prominent guidelines on the treatment of MRSA infections highlight crucial aspects for the use of vancomycin, such as the need to maintain the trough levels of the antibiotic in blood in the range 15–20 mg/L in order to optimize its efficacy and reduce
the risk of toxicity; and the concerns about its efficacy when MRSA strains have vancomycin MICs ≥ 2 mg/L. Although use of the new drugs may improve outcomes in certain circumstances, cost–benefit studies should be undertaken to justify their routine administration, since the associated incremental cost is very high.

More difficult to justify is the lack of reduction in the consumption of teicoplanin and vancomycin, the latter still remaining the most prescribed drug. The best explanation would be the routine empirical use of these glycopeptides to cover MRSA or CoNS in cases of suspected catheter-related sepsis, a practice conducted frequently in hospitals regardless of the local epidemiology or the clinical data.

Limitations of the study notably include the fact that certain drugs active against MRSA, such as tigecycline, quinupristin/dalfopristin and fosfomycin, were not analysed. This decision was taken after considering their very low consumption according to the VINCat Programme data file. Another limitation is the activity of the new drugs against other resistant Gram-positive organisms and consequently their possible use outside of MRSA infections; however, VRE are not prevalent in our centres and, according to the current guidelines, CoNS infections are rarely treated with linezolid or daptomycin. Another potential confounder not taken into account is possible variation in the case mix during the study period. The strengths of the study are data collection through a consolidated surveillance programme such as VINCat and the large number and great diversity of hospitals involved.

In conclusion, a widespread and steady increase in the consumption of new MRSA-active antibiotics was observed among acute care hospitals in Catalonia, in spite of a stable MRSA burden. This increase resulted in a significant increment of cost. Surprisingly, the consumption of old drugs remained stable. Our findings suggest that factors other than methicillin resistance may influence the use of old and new MRSA-active antibiotics in the clinical setting. These factors should be analysed in depth to introduce corrective measures if needed.

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Transparency declarations
None to declare.

Supplementary data
Tables S1, S2 and S3 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


