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Impact of hospital-wide infection rate, invasive procedures use and antimicrobial consumption on bacterial resistance inside an intensive care unit

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SUMMARY

We performed a 30-month ecological study to determine the impact of hospital-wide antibiotic consumption, invasive procedure use and hospital-acquired infections (HAIs) on antibiotic resistance in an intensive care unit (ICU). Microbiological isolates from ICU patients with established diagnosis of hospital infection were monitored throughout the study. Overall hospital consumption per 100 patient-days of piperacillin-tazobactam, fluoroquinolones and cephalosporins increased from 1.9 to 2.3 defined daily doses (DDD) ($P < 0.01$), from 4.7 to 10.3 DDD ($P < 0.01$) and from 12.1 to 16.4 DDD ($P < 0.01$), respectively. Bacterial multiresistance in ICU was identified in 31.3% ($N = 466$) of isolates, with increasing resistance demonstrated for meropenem-resistant *Klebsiella* spp. ($P = 0.01$) and meropenem-resistant *Acinetobacter* spp. ($P = 0.02$). There was a positive correlation between multiresistance rate and DDD of cephalosporins ($P < 0.01$) and fluoroquinolones ($P = 0.03$). The rate of ceftazidime-resistant *Klebsiella* spp. correlated with DDD of fluoroquinolones and cephalosporins; the rate of ceftazidime-resistant *Pseudomonas* spp. correlated with consumption of cephalosporins, and rate of meticillin-resistant *Staphylococcus aureus* (MRSA) correlated with fluoroquinolone use. During the studied period, 36.9% ($P < 0.001$) and 34.5% ($P < 0.01$) of the changing multiresistance rate in ICU was associated with use of invasive procedures and overall HAI rate, respectively. Multiresistance rates in ICU are influenced by the variation in overall HAI rate, hospital-wide invasive procedures and antibiotic consumption outside the ICU.

Introduction

Between 5% and 15% of hospital inpatients develop an infection during hospital stay. Critically ill patients in intensive care units (ICUs) are 5–10 times more likely to acquire hospital-acquired infection (HAI) than those in non-critical wards.[1,2] HAIs are increasing in prevalence due to ageing populations, more immunocompromised patients and greater use of invasive interventions. Many of these infections are associated with multiresistant bacteria.[3–6]

Resistant micro-organisms are recognised as a reason for extended length of stay, higher costs and greater morbidity and mortality in hospital settings.[4,6,7] Previous studies suggest that there is a causal association between antimicrobial usage and antimicrobial resistance.[8,9] HAIs due to multiresistant *Acinetobacter* spp. and *Pseudomonas* spp. strains are a particular problem in ICUs of tertiary care hospitals.[10] Thus, many organisations have recommended that aggregated antibacterial drug use should be monitored at local and national levels to better understand the relationship between the use of antimicrobial drugs and emerging antimicrobial resistance.[11–13]

The present study describes the relationship between antimicrobial consumption, invasive procedures and HAIs and microbial resistance in an ICU of a teaching hospital in Southern Brazil.

Methods

Setting

The study was carried out in the adult ICU of Hospital de Clínicas de Porto Alegre (HCPA), a public, tertiary care teaching hospital in

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the city of Porto Alegre, southern Brazil. This hospital has 749 beds, with 22 non-critical wards and three ICUs (adult, neonatal and paediatric). The adult ICU has 34 beds for medical and surgical patients.

Study design and definitions

Microbiological isolates identified before or after ICU admission were evaluated. Data were reviewed for patients aged ≥15 years who had been admitted to the ICU with established diagnosis of HAI, from July 2004 to December 2006.

Bacterial isolates were reviewed from the hospital electronic database and all micro-organisms were identified by the microbiology unit. The identification of bacterial species was performed according to standard laboratory protocols and susceptibility testing by disc-diffusion method, interpreted according to Clinical and Laboratory Standards Institute guidelines.[14] Only the first microbiological isolate was considered, irrespective of the body site from which the specimen was obtained or the antimicrobial susceptibility pattern.[15] Isolates of patients with diagnosis of community-acquired infections, colonisation or surveillance data were excluded.

Hospital-acquired infections were classified by the Infection Control Committee (ICC) nurse based on diagnostic criteria of the Centers for Diseases Control and Prevention.[16] The HAI general rate was calculated by computing HAIs that occur in all critical and non-critical areas, divided by the total number of patient-days on a monthly basis.

Resistance data

Bacterial multiresistance was classified according to the CDC recommendations and ICC criteria, and included the following: extended-spectrum β-lactamase (ESBL)-producing *Klebsiella* spp. and *Escherichia coli*; ceftazidime-resistant and/or carbapenem-resistant *Pseudomonas* spp.; ampicillin/sulbactam-resistant and/or carbapenem-resistant *Acinetobacter* spp.; *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp. and *Proteus* spp. resistant to all antibiotics except carbapenems; sulfamethoxazole/trimethoprim-resistant *Stenotrophomonas maltophilia*; any *Burkholderia cepacia*; vancomycin-resistant *Enterococcus* spp. and meticillin-resistant *Staphylococcus aureus* (MRSA). Isolates with intermediate susceptibility were considered resistant.[15,17]

Measures of antimicrobial use and invasive procedures

Antibiotic consumption was computed for ICU and for overall hospital (including ICU). Data on consumption of vancomycin, cephalosporins, fluoroquinolones, penicillins with β-lactamase inhibitors, carbapenems and aminoglycosides were expressed as the number of defined daily doses (DDD) per 100 patient-days on a monthly basis, as recommended by the 2005 version of the Anatomical Therapeutic Chemical (ATC) classification system and the DDD index.[18]

Information about the invasive procedures (urinary catheter and central venous catheter use, mechanical ventilation) was reviewed and classified as ICU-related and non-ICU-related. The total number of days of each of these invasive procedures was counted excluding the paediatric units (ICU, neonatal ward, and paediatric ward).

Data on antibiotic consumption and invasive procedures use were obtained from the institution's electronic database.

Statistical analysis

The bacterial multiresistance rate was calculated by dividing the number of resistant isolates for each species by the total number of bacterial isolates for each species and multiplying the quotient by 100. Linear regression was used to measure the curve trends, and Pearson's or (for non-parametric variables) Spearman's correlation coefficient (r) was used to assess the relationship between antibiotic consumption and prevalence of bacterial multiresistance. The data is reported on a quarterly basis.

A sample size of a 30 consecutive month period was estimated considering the correlation coefficient for the rate of bacterial multiresistance and antimicrobial DDD of 0.5, an α-error of 0.05 and β-error of 0.20. All collected data were stored using the Epi Info version 3.3.2 database. Data were analysed with SPSS 14.0 and STATA 10 statistical package. Statistical significance in all analyses was defined as $P < 0.05$.

The study was approved by the institution's Review and Ethics Committee.

Results

Study population

The mean ICU HAI rate from July 2004 through December 2006 was 33.3 ± 6.5 per 1000 patient-days, while the mean total hospital-wide acquired infection rate was 9.5 ± 1.0 per 1000 patient-days. The mean length of ICU stay was 5.6 ± 0.7 days; mean age of the patients in years was 58.7 ± 17.3; mean Acute Physiological Assessment and Chronic Health Evaluation (APACHE) II was 23.9 ± 9.0. Of the studied patients, 36.4% had acquired hospital infection before ICU admission.

Antibiotic consumption

From July 2004 to December 2006, the total mean antibiotic consumption for the entire hospital and ICU was 38.2 and 91.6 DDD per 100 patient-days, respectively. Total hospital consumption of piperacillin-tazobactam, fluoroquinolones and cephalosporins increased from 1.9 in the first to 2.3 DDD per 100 patient-days in the last month ($r = 0.61$, $P < 0.01$), from 4.7 in the first to 10.3 DDD per 100 patient-days in the last month ($r = 0.56$, $P < 0.01$) and from 12.1 in the first to 16.4 DDD per 100 patient-days in the last month ($r = 0.60$, $P < 0.01$) respectively. In contrast, the consumption of ampicillin-sulbactam decreased from 9.8 to 1.6 DDD per 100 patient-days ($r = -0.75$, $P < 0.01$) and aminoglycosides from 4.7 to 4.4 DDD per 100 patient-days ($r = -0.60$, $P < 0.01$) in the first and last months. No statistically significant trends were observed for carbapenem or vancomycin consumption throughout the period. Considering sole ICU antimicrobial use, only DDD of piperacillin-tazobactam and ampicillin-sulbactam changed with time, increasing from 6.8 to 9.0 DDD per 100 patient-days ($r = 0.57$, $P < 0.01$) for piperacillin-tazobactam, and decreasing from 22.0 to 3.8 DDD per 100 patient-days ($r = -0.37$, $P = 0.04$) for ampicillin-sulbactam, in the first and last months of observation.

Microbiological results

During the 30 month study period, 1490 microbiological isolates were included: 419 (28.1%) from Gram-positive bacteria [*S. aureus* (254), *Enterococcus* spp. (71), coagulase-negative staphylococci (56), *Streptococcus* spp. (24)], 866 (58.1%) from Gram-negative bacteria [*Klebsiella* spp. (179), *Pseudomonas* spp. (177), *E. coli* (126), *Acinetobacter* spp. (117), *Enterobacter* spp. (96), *Haemophilus* spp. (34), *Proteus* spp. (29), *Stenotrophomonas* spp. (28), non-identified non-fermenting Gram-negative bacilli (26), *Serratia* spp. (22), *Citrobacter* spp. (14), *Morganella morganii* (10), *B. cepacia* (5)] and 205 (13.8%) from other species [*Candida* spp. (184)]. From the 1285 bacterial isolates, 39.5% were from respiratory tract; 22.9 from

urinary tract; 16.0% from blood cultures; 9.5% from catheter-related infections; 5.8% from abdominal infections; 2.6 from surgical procedure-related infections and 3.7% from other sites.

The multiresistance rate in ICU was 31.3% (466), 45.3% (190) among Gram-positive and 31.9% (276) among Gram-negative isolates. There was a significant variation of multiresistant isolate rates with time ($r = 0.43$, $P = 0.02$), with rates ranging from 9.8% at the third month to 47.8% during the 26th month of the study.

There was a significant increase in meropenem-resistant *Klebsiella* spp., from 0.0% in the first month to 5.3% in the last ($r = 0.76$, $P = 0.01$) and for meropenem-resistant *Acinetobacter* spp., from 0.0% in the first month and 18.2% in the last ($r = 0.70$, $P = 0.02$). Conversely, ciprofloxacin-resistant *Pseudomonas* spp. reduced from 72.2% in the first to 42.9% in the last period ($r = -0.56$, $P = 0.09$).

Multiresistance rates of *Pseudomonas* spp. and *S. aureus* varied from 12.5% to 73.3% and from 60.0% to 85.2%, respectively. Resistance rates did not change significantly, being 35.0% in the first month and 31.6% in the last ($r = -0.21$, $P = 0.57$) for *Pseudomonas* spp. and for MRSA 60.0% in the first month and 85.2% in the last ($r = 0.48$, $P = 0.16$).

Relationship between antibiotic consumption and rates of resistance

Considering overall hospital antimicrobial consumption (including ICU), there was a positive correlation between bacterial multiresistance rate in the ICU and DDD of cephalosporins ($r = 0.79$, $P < 0.01$) and fluoroquinolones ($r = 0.68$, $P = 0.03$).

No correlation was found between bacterial multiresistance rate in ICU and hospital-wide consumption of aminoglycosides ($r = -0.41$, $P = 0.24$), ampicillin-sulbactam ($r = -0.44$, $P = 0.21$), piperacillin-tazobactam ($r = 0.40$, $P = 0.25$), carbapenems ($r = -0.02$, $P = 0.96$) or vancomycin ($r = -0.50$, $P = 0.14$).

Figure 1 shows the Spearman's correlation (r) between hospital-wide consumption (in DDD) of cephalosporins and fluoroquinolones and rates of MRSA, ceftazidime-resistant *Klebsiella* spp., and ceftazidime-resistant *Pseudomonas* spp. The rate of ceftazidime-resistant *Klebsiella* spp. was significantly correlated with DDD of fluoroquinolones and cephalosporins (Figure 1(A) and (B)). MRSA correlated with DDD of fluoroquinolones (Figure 1(C)) and ceftazidime-resistant *Pseudomonas* spp. correlated with DDD of cephalosporins (Figure 1(D)). Consumption of cephalosporins and fluoroquinolones correlated with the rate of ESBL-producing *Klebsiella* ($P = 0.02$).

Carbapenem consumption did not correlate with any bacterial resistance rates in our study, and fluoroquinolone consumption did not correlate with ciprofloxacin resistance among *Pseudomonas* spp. ($P = 0.38$), *Escherichia coli* ($P = 0.31$), or *Klebsiella* spp. ($P = 0.30$). Consumption of cephalosporins did not correlate with ceftazidime resistance in *E. coli* ($P = 0.84$).

Considering only antibiotic DDDs for the ICU, no correlation was observed when the association between antimicrobial consumption and multiresistance rates was analysed.

Relationship between invasive procedures and rates of resistance

During the 30 month study period, a total of 583.0 days of mechanical ventilation, 400.5 days of urinary catheter and 176.4 days of central venous catheter were recorded. No correlation was found when we analysed the number of invasive procedures performed during ICU stay and antimicrobial resistance in ICU for invasive urinary catheter use ($r = 0.16$, $P = 0.40$), for central venous catheter ($r = 0.33$, $P = 0.07$) and for mechanical ventilation use ($r = 0.22$, $P = 0.25$). When we analysed the total number of days of invasive procedures in ICU, there was no correlation with the multiresistance rate ($r = 0.28$, $P = 0.13$).

We found a positive correlation between urinary catheter use and multiresistance rate in ICU ($r = 0.42$, $P = 0.02$), and for central venous catheter and multiresistance rate in ICU ($r = 0.50$, $P < 0.01$). Taken together, 36.9% of the variation of multiresistance rate in ICU was associated with whole hospital (except ICU) invasive procedure use ($R^2 = 0.37$; $P < 0.001$).

Relationship between HAI and rates of resistance

We also explored the correlation between hospital-wide infection rate and bacterial multiresistance inside the ICU. In the period studied, 34.5% of the variation of the bacterial multiresistance rate in ICU was associated with the variation of hospital general infection rate ($R^2 = 0.34$; $P < 0.01$).

Discussion

Antibiotic exposure is an important risk factor for bacterial resistance in hospitalised patients.[19–21] In our study, increased use of fluoroquinolones correlated with the emergence of ESBL-producing *Klebsiella* isolates, and also with MRSA. We also recorded a significantly positive correlation of cephalosporin use and increasing rate of ESBL-producing *Klebsiella*. Others have reported the association of fluoroquinolones with emergence of ciprofloxacin-resistant *P. aeruginosa*, MRSA and ESBL, and demonstrated an association between cephalosporin use and increasing rates of resistance in *K. pneumoniae*, *E. coli*, *Enterobacter* spp. and *P. aeruginosa*.[8,22–25]

We observed a significant correlation between antimicrobial use and bacterial multiresistance rates when antibiotic consumption for the whole hospital was considered. The same findings were not observed when only DDD rates related to ICU antibiotic consumption were included. These findings may have several potential explanations. Firstly, the antibiotic pressure of the whole hospital may represent a more explanatory variable comparatively to the DDD of the ICU alone. Second, generally critically ill patients acquire infection and are exposed to antimicrobials before the ICU admission. Infectious agents with a substantial incubation period or prolonged carrier state, such as MRSA or VRE, can be introduced into the ICU ward if undetected before ICU admission, since patients may not exhibit symptoms of these diseases until they are at higher risk in an ICU.

As stated above, the association between antibiotic pre-exposure and development of resistance is well established, but one of the interesting findings in this study is the positive correlation between the hospital-wide acquired infection rate and hospital-wide (except ICU) invasive procedures use and the bacterial multiresistance rate inside the ICU. This finding highlights the importance of patient transfer with established infection or resistant bacteria between wards and ICU. More than one-third of the multi-drug resistant bacteria rate in the ICU could be addressed through infection control measures implemented outside the unit. Attempts to reduce use of invasive procedures outside the ICU might have an impact on bacterial multiresistance rates inside the ICU.[26–28]

In the survey by Climo *et al.*, two-thirds of central venous lines, an important known risk factor for bloodstream infections, were identified in non-ICU patients.[26] Marschall *et al.* showed that despite the lower central-line catheter utilisation, the central venous catheter infection rate outside ICU had similar rates to these related infections inside ICU.[27] Outside ICU, Vomberg *et al.* found a rate of 4.3 infections per 1000 central venous catheters and 6.8 infections per 1000 urinary catheter-days.[28] All these data suggest that more effort should be made in terms of infection prevention outside of high risk wards such as ICUs.

This study may not address all multifactorial causes of emergence and hospital dissemination of resistance. Ecological studies have some limitations compared to individual level analysis when

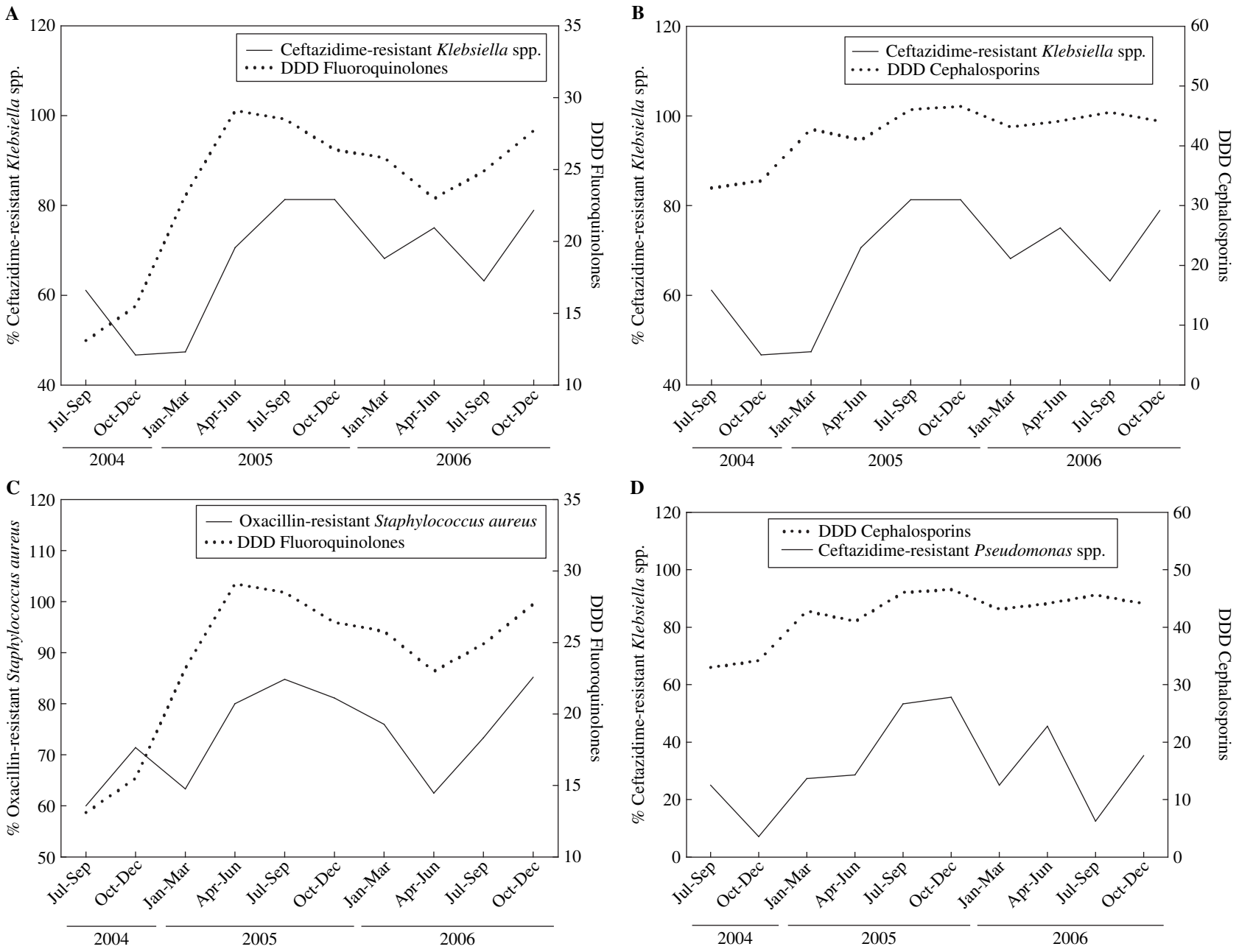

Figure 1. Relationship between hospital-wide antibiotic consumption and bacterial resistance rates inside the intensive care unit. (A) Ceftazidime-resistant *Klebsiella* spp. and defined daily doses (DDD) per 100 patient-days of fluoroquinolones (Spearman's $r = 0.70$, $P = 0.02$). (B) Ceftazidime-resistant *Klebsiella* spp. and DDD per 100 patient-days of cephalosporins (Spearman's $r = 0.77$, $P = 0.01$). (C) Oxacillin-resistant *Staphylococcus aureus* and DDD per 100 patient-days of fluoroquinolones. (D) Ceftazidime-resistant *Pseudomonas* spp. and DDD per 100 patient-days of cephalosporins (Spearman's $r = 0.65$, $P = 0.04$).

addressing bacterial multiresistance in hospital settings. It is not possible to evaluate time as an important exposure variable related to the emergence of multiresistance, and the 'ecological bias' or the analysis of aggregated data may be limited by the failure of level-effect estimates to reflect the biological effect at the individual patient level.[20] Nevertheless, the method adopted should address population phenomena such as antibiotic pressure and its impact on multiresistant bacteria.

Our results underline the importance of ecological approaches addressing the 'institutional epidemiological weight' of compartments (e.g. ICU and non-critical wards) in dissemination or maintenance of outbreaks and endemic levels of multiresistant bacteria. Hartley *et al.* mathematically estimated the contribution of a specific population ('compartment') in a specific epidemic or outbreak, comparing the role ('epidemiologic weight') of two institutions (a short-term holding jail and a tertiary care hospital) to incident MRSA carriage in a population.[29] They studied the transmission of pathogens between institutions but this model could be also applied to one particular area within an individual institution.

In summary, the variation in bacterial multiresistance rate in ICUs appears to be related to the overall HAI rate in the hospital, invasive procedure usage and antibiotic consumption outside ICU. This finding underlines the relevance of implementing hospital-wide approaches to HAI surveillance and antibiotic control, or the importance of identifying areas at risk of transmission of resistant pathogens within an institution.

Conflict of interest statement
None declared.

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