



## Letters to the Editor

## Impact of extended-spectrum $\beta$ -lactamases and carbapenem-resistant Gram-negative infections on sepsis mortality at the emergency department: a cohort study



Sir,

Sepsis is one of the leading causes of mortality worldwide [1]. Despite efforts for early detection and guidelines for sepsis treatment, approximately one-third of patients die one month after the diagnosis [2]. When sepsis is diagnosed at hospital admission or within the first 48 h after emergency department arrival, choice of antimicrobial regimen usually relies on probable bacteria involved according to infection site, local community resistance profiles, previous use of antibiotics, or exposure to healthcare facilities. The increase in multidrug-resistant bacterial infections in patients arriving from the community has imposed a greater challenge in this choice. Infections by carbapenem-resistant Gram-negative isolates have been particularly worrisome in developing countries, where the higher rates of these pathogens have been reported [3].

In this retrospective cohort we evaluated risk factors for 30-day mortality in patients diagnosed with sepsis and at least one organ dysfunction or septic shock in the first 48 h after emergency admission, with emphasis on the impact of infections by extended-spectrum  $\beta$ -lactamase (ESBL) producers and carbapenem-resistant Gram-negatives.

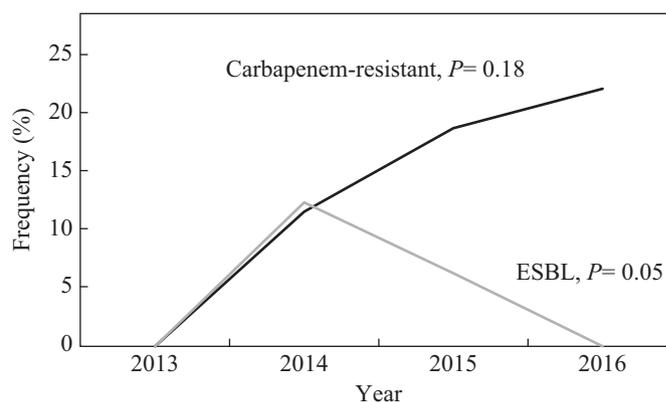
Patients aged  $\geq 18$  years were included from November 2013 to May 2016, in a 593-bed hospital in Porto Alegre, Brazil. A second sepsis episode was analysed if it happened two weeks after the first one or if a different pathogen (or infection site) was documented. Variables possibly related to mortality were assessed: demographics (age, sex), comorbidities, Charlson comorbidity index, severity of the disease (quick Sequential Organ Failure Assessment (SOFA), septic-shock, mechanical ventilation), infection site, bacterial isolates and antibiotic regimen prescribed [1,4]. Bacterial identification and antimicrobial susceptibility tests were performed using Vitek-2 (bioMérieux, Marcy l'Etoile, France) automatized system and interpreted according to Clinical and Laboratory Standards Institute criteria [5].

Statistical analysis was performed using SPSS 18.0 for Windows. Univariate analyses were performed using Fisher's exact

test or Cochran–Armitage test ( $\chi^2$  for trend) for categorical variables and Student's *t*-test or Mann–Whitney *U*-test for continuous variables. All tests were two-tailed and  $P < 0.05$  was considered statistically significant. Cox regression was performed including variables with  $P \leq 0.20$  in univariate analysis in a forward stepwise model and maintained variables with  $P \leq 0.05$ .

In all, 673 sepsis episodes were included for analysis, within a total of 637 patients. Thirty-day mortality was 179 (26.6%) and occurred in a median time of 11 (6–20) days. Positive cultures were obtained from 258 (38.3%) patients; 191 (74.0%) isolated Gram-negative bacteria. Among these, 18 (9.4%) recovered ESBL producers, and 27 (14.1%) carbapenem-resistant bacteria. All ESBL producers were Enterobacteriaceae. Among carbapenem-resistant bacteria, 13 (48.1%) were *Klebsiella pneumoniae*, followed by *Acinetobacter baumannii* 11 (40.7%) and *Pseudomonas aeruginosa* 3 (11.1%). Urinary tract was the most frequent isolation site for both resistance profiles. The distribution of ESBL and carbapenem-resistant strains with respect to time is shown in Figure 1. Although there was an absolute increase in the prevalence of carbapenem-resistant Gram-negatives over time, it was not statistically significant. ESBL infection prevalence decreased after 2014.

Hospitalization within the last 90 days occurred in patients infected by: nine (50%) of 18 ESBL, 17 (63.0%) of 27 carbapenem-resistant Gram-negatives, and 161 (25.6%) of 628 of other isolates ( $P < 0.01$ ). Among patients with carbapenem-resistant infections, seven (25.9%) had been previously treated with these drugs and 10 (37.0%) had isolated the same bacterial phenotype in clinical samples or vigilance swabs before. For



**Figure 1.** Proportion of extended-spectrum  $\beta$ -lactamase (ESBL) and carbapenem-resistant isolates among Gram-negative sepsis diagnosed in the first 48 h of hospital admission ( $N = 191$ ).

seven (25.9%) patients, there was no registry of previous exposure to healthcare facilities.

Among patients who recovered a microbiological isolate, a lower rate of in-vitro susceptible empiric therapy was administered to those with infections by ESBL (50%) and carbapenemase-producing Gram-negatives (26.9%) compared to other patients (77.4%) ( $P < 0.01$ ). Patients with carbapenem-resistant isolates had significantly higher 30-day mortality in univariate analysis: 13 (48.1%) of 27 versus 166 (25.7%) of 646 ( $P = 0.02$ ). Older age ( $P = 0.04$ ), cancer ( $P = 0.04$ ), HIV infection ( $P = 0.02$ ), cirrhosis ( $P = 0.04$ ), septic shock ( $P < 0.01$ ), and higher quick-SOFA ( $P = 0.04$ ) were associated with 30-day mortality in the final Cox regression model.

In our study, Gram-negative bacteria were the leading cause of infections in septic patients. There was a growing prevalence of carbapenem-resistant Gram-negatives over time, associated with worse outcomes. As expected, most of these patients had exposure to healthcare facilities, but only a minority of them had previously received carbapenem or had yielded isolates of these bacteria. These data raise the concern about the spread of multi-resistant organisms in healthcare facilities even without previous carbapenem exposure. Delays in adequate treatment plus scarce and/or suboptimal antibiotic options for the management of these infections may explain their higher mortality rate [6,7]. The factors that remained in our final multivariate model underline that severity status at diagnosis and comorbidities play a key role in clinical response.

This study warns us about the growing prevalence of multi-resistant infections in patients arriving at the hospital. Rapid tests for detection of carbapenemases could be a valuable tool for guiding therapy. Meanwhile, we need strict vigilance of Gram-negative resistance and adjustment of empiric treatment accordingly.

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### Conflict of interest statement

None declared.

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## Value of a hospital-wide point prevalence survey of carbapenemase-producing Enterobacterales – low-level prevalence confirmed



Sir,

Carbapenemase-producing Enterobacterales (CPE) are associated with limited treatment options, and increased morbidity and mortality [1,2]. Beaumont Hospital (BH) is an 820-bed tertiary hospital and is the Irish national referral centre for neurosurgery, renal transplantation and cochlear implantation. BH operates a risk-based CPE surveillance programme including admission and weekly rectal screening in high-risk ward areas (critical care, haematology and renal transplant), screening of inpatient contacts of new cases, non-domestic hospital transfers and interhospital transfers to