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Major article

Identification of temporal clusters and risk factors of bacteremia by nosocomial vancomycin-resistant enterococci

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Background: This study aimed to evaluate a different methodology for addressing the evolution of nosocomial bacteremia by vancomycin-resistant enterococci (VRE) in a hospital setting.
Methods: In this retrospective cohort study, data were collected from the date of first registration up to December 2008 from the electronic medical records of patients with VRE bacteremia in a school hospital.
Results: Thirty cases of VRE bacteremia and 274 cases of vancomycin-susceptible enterococci (VSE) bacteremia were identified. The average age of the patients was 56 years. The rates of *Enterococcus faecium* and *Enterococcus faecalis* in the hospital's intensive care unit (ICU) and wards showed no statistically significant differences. The risk of acquiring VRE bacteremia was at least 3-fold higher in the ICU than in the wards. The risk of death was 2.73-fold higher in patients with VRE bacteremia compared with those with VSE bacteremia. Only one temporal cluster statistically significant of VRE bacteremia was found in the study period.
Conclusions: The identification of temporal clusters can be an important tool to optimize health actions and thereby reduce the burden of operating costs.

Enterococci are gram-positive bacteria with ability to develop either aerobiosis or anaerobiosis, the latter optionally. More than 20 species of this bacterium have been described, with *Enterococcus faecalis* and *Enterococcus faecium* the most common in human infections. Enterococci are present throughout the entire gastrointestinal tract (their main reservoir), from the mouth to the anus. They also can colonize the skin, vagina, and airways. They are frequently associated with infections in patients undergoing invasive processes, as central venous catheters and urinary probes. They are a common cause of urinary infections, and have been associated with other infections as well, including cholecystitis, cholangitis, peritonitis, septicemia, endocarditis, meningitis, and wound infections.

The first cases of vancomycin-resistant enterococci (VRE) were isolated in Europe in 1988,[1] and other registrations soon followed. In Brazil, VRE was first documented in 1996, with *E faecium* isolated in blood culture.[2] Since the first reported cases, VRE infections have been increasing worldwide. These infections are intrinsically related to both the rise in mortality during hospitalization and the high costs of inpatient care.[3]

Few previous studies have addressed the determination of these risk factors together with the identification of the exact time when the dissemination of nosocomial VRE could be statistically significant. The present study aimed to identify temporal clusters of nosocomial VRE bacteremia and to evaluate risk factors for bloodstream infection and death from VRE in relation to vancomycin-susceptible enterococci (VSE), with the goal of optimizing control actions inside the hospital.

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Conflict of interest: None to report.

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METHODS

Data collection

Information was obtained from the computerized database from a school hospital in São José do Rio Preto, Brazil. The first case of VRE (caused by *E faecalis*) was diagnosed on August 28, 1998. Subsequently, 304 cases of either VRE or VSE in the blood were documented between September 30, 1998, and December 12, 2008. The following data were collected: sex, age, comorbidity, hospitalization time and place, previous antibiotics used and duration of use, albumin levels, and previous radiotherapy, chemotherapy, corticosteroid therapy, and invasive procedures.

Autochthonous and imported infections

Only cases of nosocomial VRE in the blood documented by hemoculture were analyzed in this study. Following a previous study,[4] cases of enterococci bacteremia were classified as community-acquired when diagnosed within the first 48 hours of hospitalization. Unit infections were defined as those diagnosed after at least 72 hours of admission to the unit, and extra-unit infections were defined as infections present at the moment of the admission and, at the same time, within 48 hours of admission in another unit. In this case, the registration of that infection was computed for the patient's unit of origin.

Laboratory criteria for VRE characterization

For the sensitivity test, isolated enterococci from the hospitalized patients were sowed in Müller-Hinton culture to 37°C and then read after 24 hours. The following antibiotics are rountinely tested for *Enterococcus* spp: ampicillin, ciprofloxacin, gentamicin, linezolid, penicillin, streptomycin, teicoplanin, vancomycin, and, in some cases, gatifloxacin and moxifloxacin.

To a minimum inhibitory concentration (MIC) of $\leq$4 μg/mL, enterococci is defined as vancomycin-susceptible. An MIC >4 μg/mL and <32 μg/mL is defined as intermediate susceptibility, and an MIC $\geq$32 μg/mL is defined as vancomycin-resistant, as described previously.[5]

Statistical analysis

Using a retrospective cohort study, the index case of VRE was identified in the hospital. The time considered in this case was determined from the date of study initiation. The hospital units with at least 1 case of VRE in the blood were registered, and the patients with VSE in the same unit as well as in the same time interval were included in the comparison group. The study's closing date was December 12, 2008.

Fisher's exact test or the Pearson χ^2 test was used to compare proportions in the period among species of VRE versus ending (death or hospital discharge), species versus unit (intensive care unit [ICU] or ward), and species versus sensibility to ampicillin, linezolid, and teicoplanin at a 5% significance level. Analyses were performed with StatsDirect version 2.7.2 (StatsDirect, Cheshire, UK).

Binary logistic regression, using R version 2.8.1 (R Project for Statistical Computing, Vienna, Austria), was applied to estimate the risk of death in patients with VRE and VSE and the risk of VRE acquisition in the ICU was used for this purpose.

The Kulldorff temporal scan statistic was used to observe whether the episodes were randomly distributed along the period of the study, and to identify the statistically significant temporal clusters. The analysis was performed using SaTScan version 7.0.3, which creates windows that are transported systematically along a time line to allow identification of significant clusters of infection. Here 100,000 Monte Carlo reapplications were used. The maximum duration of the temporary windows was defined as 50% of the study period. For each date, SaTScan determines a reasonable probability (likelihood ratio test) to evaluate whether the infections are more prevalent in the window than out of it. A Bernoulli model was used, in which the nullity hypothesis takes into account that the expected number of cases in each window was proportional to the number of cases in the entire period.

This study was approved by the Committee of Ethics in Research of the Federal University of São Paulo (registration CEP 1562/08).

RESULTS

In our hospital, the first case of VRE (*E faecalis*) was diagnosed on August 28, 1998. It was isolated in the urine of a 25-year-old patient with AIDS. Cases with positive hemocultures for that pathogen were identified only later, however. Between September 30, 1998, and December 12, 2008, 304 cases of either VRE or VSE in the blood were documented, of which only 30 were due to VRE, including 22 cases (73.3%) in men and 8 cases (26.7%) in women (male:female ratio of ~2.75:1).

The mean age of the 30 patients with VRE bacteremia was 56 ± 20.9 years (range, 0-80 years), with 50% aged 62-80 years. *E faecium* was isolated in 19 blood samples (63.3%), *E faecalis* was isolated in 9 samples (30.0%), and *Enterococcus* spp was isolated in 2 samples (6.7%) of hospitalized patients in intensive care units or other wards. Twenty-three patients (76.7%) died, and only 7 (23.3%) were discharged from the hospital.

Of the 30 cases of VRE bacteremia diagnosed in hospitalized patients, 22 (73.3%) were registered in the ICU and the other 8 (26.7%) were detected in wards. Causes of hospitalization in the patients with VRE bacteremia included pneumonia in 9 (30.0%), hepatic cirrhosis in 2 (6.7%), congestive heart failure in 2 (6.7%), acute pancreatitis in 2 (6.7%), other causes in 7 (23.2%), and no information in 8 (26.7%).

There was no statistically significant difference in the proportions of patients in the ICU and wards between the patients with *E faecium* (ICU: 73.7% [n = 14]; wards: 26.3% [n = 5]) and the patients with *E faecalis* (ICU: 66.7% [n = 66]; wards: 33.3% [n = 3]) ($P > .99$, Fisher's exact test).

The mean duration of hospitalization in the patients with VRE bacteremia was 36 ± 22.5 days (range, 2-95 days), with 50% hospitalized for up to 32 days. The mean duration of hospitalization in the suspected unit of origin of VRE transmission was 33.8 ± 21.0 days (median, 30 days; range, 2-70 days).

No patient underwent radiotherapy, but 25 (83.3%) received chemotherapy, 22 (73.3%) were treated with corticosteroids, and 15 (50.0%) underwent hemodialysis before being diagnosed with VRE in the blood. Twenty-seven patients had undergone some type of invasive procedure (Table 1).

The majority of the patients with VRE bacteremia had a serum albumin level below the reference value (newborns: 2.8-4.4 g/dL; children: 3.8-5.4 g/dL; adults: 3.4-5.4 g/dL). In 85% of these patients, the level was <3.2 g/dL, and 25% had a level of 1.1-1.9 g/dL.

VRE detected in hemocultures demonstrated differing sensitivity profiles for the various antibiotics tested (Table 2). Some antibiotics were not tested because of laboratory routine and a lack of available test kits. The finding that 28 cases of VRE (93.3%) also demonstrated teicoplanin resistance (Table 2) has drawn some attention.

The prevalence of sensitivity to ampicillin was higher in patients with *E faecalis* infection compared with patients with *E faecium*