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Major article

Bacteremia caused by multidrug-resistant bacteria in a French university hospital center: 3 years of collection

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Key Words:
Bacteremia
Bloodstream infection
Multidrug resistance
Mortality

Background: The aim of the study was to describe the profile of patients and the characteristics of all bacteremias caused by multidrug-resistant (MDR) bacterial strains in a teaching hospital and to assess the mortality related to these events.

Methods: A monocentric retrospective observational cohort study was conducted. All patients with bacteremia caused by MDR bacteria between 2011 and 2013 were included. The characteristics of patients and bacteremias, antibiotic therapy within the first day, and 30-day mortality were collected from the electronic medical records database.

Results: A total of 228 patients were included with bacteremias caused by *Enterobacteriaceae*-producing extended-spectrum β-lactamase (n = 102), *Enterobacteriaceae* overproducing AmpC β-lactamase (n = 59), carbapenem-resistant *Enterobacteriaceae* (n = 3), ceftazidime- or carbapenem-resistant *Acinetobacter baumannii* (n = 2), ceftazidime- or carbapenem-resistant *Pseudomonas aeruginosa* (n = 23), methicillin-resistant *Staphylococcus aureus* (n = 40), and vancomycin-resistant *Enterococcus* (n = 2). The median Charlson comorbidity score was 6. Inappropriate antibiotic therapy was prescribed in 41.7% of bacteremias, and 30-day mortality was 23%. For 20.9% of the patients who had had a positive bacteriologic sample in the preceding 2 months, the initial antibiotic therapy was inappropriate.

Conclusion: In this cohort of bacteremia patients, a high rate of mortality and numerous patient comorbidities were observed. Taking greater account of antecedents of MDR bacterial infections could improve the rate of appropriate initial antibiotic therapy.

The incidence of multidrug-resistant (MDR) bacteria has been persistently increasing for many years.[1] In the same period, the prevalence of bacteremia in France has also been rising, which can be explained in part by an increase in patients with risk factors and comorbidities.[2] In 2012, bacteremia accounted for the fourth most frequent infection in the hospital patient population according to the French National Prevalence Survey of Nosocomial Infections.[2] The survey also highlighted that the bacteria isolated in bacteremia were more often MDR bacteria than in other infectious sites.[2]

Several studies have demonstrated the growth in fatal outcomes from bacteremia caused by MDR bacterial infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA),[3] resistant *Pseudomonas aeruginosa*,[4] extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae*,[5,6] and vancomycin-resistant *Enterococcus*,[7] compared with drug-sensitive bacteria. This excess mortality seems to be caused by a combination of host, bacteria, and treatment factors.[8]

The aim of this study was to describe the profile of patients and the characteristics of bacteremias caused by MDR bacterial strains in a teaching hospital. Secondary objectives were to identify the risk factors of mortality at 30 days and identify the risk factors leading to inappropriate initial antibiotic therapy.

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MATERIALS AND METHODS

Patient inclusion and characteristics

This was a monocentric retrospective observational cohort study. We screened all patients with suspected bacteremia caused by MDR bacteria occurring in our university hospital (2,200 acute and long-term beds) in France between January 1, 2011, and December 31, 2013.

The MDR bacteria included were MRSA, vancomycin-resistant *Enterococcus*, ceftazidime- and carbapenem-resistant *Acinetobacter baumannii*, ceftazidime- and carbapenem-resistant *P aeruginosa*, ESBL-producing *Enterobacteriaceae*, AmpC overproducing *Enterobacteriaceae*, and carbapenem-resistant *Enterobacteriaceae*.

The characteristics of each case were collected from the electronic medical records database by the first author. Based on these data, the Charlson comorbidity score[9] was calculated for each patient. This score is the sum of the subscores assigned to each condition and age. A high Charlson score indicates a greater risk of mortality at 10 years. We also collected the Simplified Acute Physiology Score II[10] from the summary of hospitalization of patients admitted to the intensive care unit (ICU) during the bacteremia episode. This score depends on both laboratory parameters and clinical evaluation during the first 24 hours after ICU admission. Most of the characteristics of our cohort of patients with bacteremia are shown in Table 1.

Table 1
Characteristics of patients with bacteremia

Variable	All patients (N = 228)	Patients at 30 d: Alive (n = 171)	Patients at 30 d: Dead (n = 51)	*P* value
Age (y)				.004
0–14	7 (3.0)	6 (3.5)	1 (2.0)	
15-64	82 (36.0)	72 (42.1)	9 (17.6)	
≥65	139 (61.0)	93 (54.4)	41 (80.4)	
Male	143 (62.7)	108 (63.2)	33 (64.7)	.84
Obesity (n = 214)	35 (16.4)	30 (18.5)	5 (10.9)	.22
Comorbidity				
Solid tumor	89 (39.0)	59 (34.5)	25 (49.0)	.06
Hematologic tumor	33 (14.5)	25 (14.6)	7 (13.7)	.87
Diabetes	71 (31.1)	53 (31.0)	15 (29.4)	.83
Chronic respiratory failure or COPD	34 (14.9)	24 (14.0)	9 (17.6)	.52
Chronic renal failure	66 (28.9)	48 (28.1)	16 (31.4)	.65
Liver disease	29 (12.7)	16 (9.4)	12 (23.5)	.007
Charlson comorbidity score				.004
≤2	33 (14.5)	31 (18.1)	2 (3.9)	
3-4	35 (15.3)	30 (17.6)	4 (7.9)	
≥5	160 (70.2)	110 (64.3)	45 (88.2)	
Immunosuppression				
Immunosuppressive treatment	39 (17.1)	34 (19.9)	5 (9.8)	.10
Corticosteroid treatment	21 (9.2)	16 (9.4)	5 (9.8)	>.99
Chemotherapy	37 (16.2)	30 (17.5)	7 (13.7)	.52
Colonization (n = 98)*	43 (43.9)	35 (46.1)	8 (38.1)	.52

NOTE. Values are n (%) or as otherwise indicated.
COPD, chronic obstructive pulmonary disease.
*Colonization or bacteriologic sample positive by the same multidrug-resistant bacterium documented within 2 months prior to the bacteremia episode.

Bacteriologic methods

Bacterial strains isolated in the samples were identified using a VITEK 2 system (Biomérieux, Marcy l'Etoile, France). Antibiotic susceptibility was tested using the VITEK2 system or the disk diffusion method. Minimal inhibitory concentration (MIC) breakpoints were based on the French guidelines in effect at the time of sampling.[11] Confirmation and phenotypic typing of the third-generation cephalosporin (3 GC) resistance mechanism were carried out using a specific disk diffusion method recommended by the national guidelines.[11] ESBL was characterized by a synergistic effect between an amoxicillin-clavulanate acid disk or ticarcillin-clavulanate acid disk and 3 GC disks. 3 GC resistance through AmpC overproduction was detected using the same disk diffusion method but with the addition of 250 mg/l cloxacillin in the culture medium, which restores 3 GC susceptibility. If a carbapenem-resistant strain was suspected with the VITEK 2 system, disk diffusion tests and exact MIC determination using Etest strips (Biomérieux, Marcy l'Etoile, France) were performed for confirmation. If carbapenem resistance was confirmed, the strain was sent to the French National Reference Center for Antibiotic Resistance to confirm and precisely identify the resistance mechanism using the Carba Nordmann-Poirel Test and polymerase chain reaction (in-house techniques for the national reference center). Resistant strains of *S aureus* (ie, MRSA) were identified by the VITEK 2 system. Confirmation of methicillin resistance was performed using the disk diffusion method (cefoxitin and moxalactam disks) completed in case of discordance by PBP2a detection by immunochromatography (Alere PBP2a Culture Colony Test; Alere, Jouy-en-Josas, France). *P aeruginosa* and *A baumannii* resistance were investigated with the disk diffusion test and MIC determination using Etest strips. Vancomycin-resistant *Enterococcus* strains were confirmed by identification of *vanA/vanB* genes using a commercial polymerase chain reaction system (Xpert vanA/vanB; Cepheid, Maurens-Scopont, France).

Definitions

Bacteremia was defined as at least 1 positive blood culture for 1 of the bacteria studied. The original source of the bacteremia was evaluated using bacteriologic sampling at the presumed source and medical reports of clinical examination. In cases of discrepancy, the cases were discussed with a second physician.

For each case the site of acquiring the infection was sought. If this could not be accurately determined and bacteremia occurred >48 hours after hospitalization admission, it was considered hospital acquired. If the onset of bacteremia was <48 hours after hospital admission and if ≥1 of the criteria defined by Friedman et al[12] were met (intravenous chemotherapy or hemodialysis during the last 30 days, home intravenous therapy or wound care during the last 30 days, hospitalization for at least 2 days during the last 90 days, residence in a long-term care facility) then the bacteremia were judged as being health care associated. In all other cases the bacteremia was considered community acquired. Recurrent bacteremia was defined as a new bacteremia episode by the same or another MDR strain during the study period after a negative blood culture window.

The patient's clinical status was mainly judged according to medical reports. In cases of missing information the following definitions were applied: severe sepsis was defined as blood lactate >4 mmol/L, organ dysfunction, and hypotension <90/40 mmHg before fluid resuscitation; and septic shock was persistent hypotension despite fluid resuscitation requiring vasopressive drugs.[13]

Variable colonization was defined as a positive bacteriologic sample of the same bacterium as the one identified in bacteremia in the previous 2 months, without intercurrent negativity. This variable combined previous positive bacteriologic samples with the same bacterium, related either to bacterial colonization or to an early antecedent of infection.

Information on antibiotic therapy was collected 1 day after the first positive blood culture. The appropriateness of antibiotic