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Prospective Multicenter Study of the Impact of Carbapenem Resistance on Mortality in *Pseudomonas aeruginosa* Bloodstream Infections

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The impact of antimicrobial resistance on clinical outcomes is the subject of ongoing investigations, although uncertainty remains about its contribution to mortality. We investigated the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bacteremia in a prospective multicenter (10 teaching hospitals) observational study of patients with monomicrobial bacteremia followed up for 30 days after the onset of bacteremia. The adjusted influence of carbapenem resistance on mortality was studied by using Cox regression analysis. Of 632 episodes, 487 (77%) were caused by carbapenem-susceptible *P. aeruginosa* (CSPA) isolates, and 145 (23%) were caused by carbapenem-resistant *P. aeruginosa* (CRPA) isolates. The median incidence density of nosocomial CRPA bacteremia was 2.3 episodes per 100,000 patient-days (95% confidence interval [CI], 1.9 to 2.8). The regression demonstrated a time-dependent effect of carbapenem resistance on mortality as well as a significant interaction with the Charlson index: the deleterious effect of carbapenem resistance on mortality decreased with higher Charlson index scores. The impact of resistance on mortality was statistically significant only from the fifth day after the onset of the bacteremia, reaching its peak values at day 30 (adjusted hazard ratio for a Charlson score of 0 at day 30, 9.9 [95% CI, 3.3 to 29.4]; adjusted hazard ratio for a Charlson score of 5 at day 30, 2.6 [95% CI, 0.8 to 8]). This study clarifies the relationship between carbapenem resistance and mortality in patients with *P. aeruginosa* bacteremia. Although resistance was associated with a higher risk of mortality, the study suggested that this deleterious effect may not be as great during the first days of the bacteremia or in the presence of comorbidities.

Pseudomonas aeruginosa is a leading cause of nosocomial infections, which are often severe (26, 43) and difficult to treat because of their limited susceptibility to antimicrobial agents (35) and the frequent emergence of antibiotic-resistant mutants during therapy (8). Factors related to the host, the organism, and the treatment may increase mortality. With regard to the host, the severity of the underlying disease may be synergistic with infection due to resistant organisms; concomitantly, increased virulence could explain the adverse impact of resistant pathogens on clinical outcomes, although this association has not been demonstrated to date. In addition, factors such as decreased antibiotic effectiveness or a delay in the initiation of therapy may contribute to adverse outcomes in patients infected by resistant pathogens (17).

The problem of antibiotic-resistant organisms is increasing (18), and the impact of antimicrobial resistance on clinical outcomes is the subject of ongoing investigations (2, 5, 9, 15, 25–28, 32, 33, 40, 41, 43), although its contribution to mortality remains uncertain. Measurements of its impact on patients are, by necessity, derived essentially from observational studies, and therefore, an adequate control of confounding variables is essential. The choice of possible confounders is usually based only on the statistical significance of the association between them and the exposure; thus, the classical criteria of confounding, also based on the relationship with the outcome and the exposure-outcome pathway, are usually ignored (24).

Carbapenems are commonly used as first-line agents for nosocomial infections, since their spectrum includes *P. aeruginosa*, which is high on the list of Gram-negative pathogens frequently isolated (37). Nevertheless, carbapenem-resistant and multidrug-resistant *P. aeruginosa* strains are being increasingly recognized (18, 39), and several studies have suggested higher mortality rates among patients infected by nonsusceptible *P. aeruginosa* strains (2, 25, 26, 28, 40, 41), although the real effect on mortality in *P. aeruginosa* bacteremia is still unknown. Furthermore, a study performed at one of the participating hospitals (40) showed that patients with carbapenem-resistant *P. aeruginosa* (CRPA) bacteremia had similar attributable mortality but slow initial mortality compared to patients infected with susceptible strains. This

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knowledge can guide antibiotic policy away from aggressive empirical therapy and the associated adverse events, increased costs, and increased selective pressure for more antibiotic resistance.

We designed a prospective, multicenter, large-scale, observational study of patients with *P. aeruginosa* bacteremia, with the main objective of investigating the impact of carbapenem resistance on mortality.

MATERIALS AND METHODS

Setting and design. Ten public hospitals located in four areas of Spain (Andalusia, the Balearics, Cantabria, and Catalonia) participated in the study between January 2008 and December 2009. All adult patients (>18 years old) with bacteremia due to *P. aeruginosa* were recruited prospectively through daily reviews of blood culture results at the participating centers. Episodes with polymicrobial bacteremia were excluded. Patients were monitored for 30 days after the first positive blood culture, and the registered event was death. Bacteremia occurring more than 14 days after the first positive blood culture was considered a new episode. The study was approved by the local ethics committees of the participating centers.

Variables and definitions. The following data were recorded: age and sex; comorbidities and severity of underlying diseases, calculated by using the Charlson comorbidity index (10); severity of illness, estimated by the simplified acute physiology score (SAPS II) for intensive care unit (ICU) patients (34); presence of neutropenia (absolute granulocyte count of <500 granulocytes/ml) and use of immunosuppressive therapy (chemotherapy, radiotherapy, and/or immunosuppressive drugs during bacteremia presentation); source of bacteremia (21); severity of acute illness at presentation according to the Pitt bacteremia score (11); presence of septic shock or severe sepsis and multiorgan dysfunction syndrome (MODS) at presentation and at 48 h (3); and antimicrobial treatment received.

CRPA was defined as isolates with imipenem and/or meropenem MICs of ≥8 mg/liter (Clinical and Laboratory Standards Institute [CLSI] intermediate and resistant categories). Bacteremia was defined as being nosocomially acquired when the infection occurred more than 48 h after admission to the hospital. Episodes of community-acquired bacteremia were further classified as being health care associated according to criteria described previously by Friedman et al. (20). The source of bacteremia was divided into two categories: low risk, including bacteremias of urinary tract and vascular catheter origins, and high risk, including all other sources (27). Empirical antimicrobial therapy was considered adequate when an antimicrobial regimen that included an active antimicrobial was administered within 24 h of the extraction of the blood sample and before susceptibility was known; aminoglycoside monotherapy was considered an inadequate treatment for *P. aeruginosa* pneumonia. Definitive antimicrobial therapy was considered therapy administered according to susceptibility results. A delay in adequate antimicrobial therapy was defined as the time from bacteremia until the administration of the empirical or definitive adequate therapy. Additional therapy was defined as procedures required to control the source of bacteremia (removal of vascular or urinary catheters as well as surgical or percutaneous drainage of collections).

Microbiological studies. The blood isolates were studied at the participating centers and sent to a reference laboratory (Servicio de Microbiología, Hospital Universitario de Bellvitge, Barcelona, Spain). *P. aeruginosa* strains were identified and tested for their antimicrobial susceptibilities by individual laboratories using standard techniques. In the reference laboratory, the antibiotic susceptibilities of 606 available isolates were confirmed by the disk diffusion method (12). CLSI criteria (13) were used to define susceptibility or resistance to the following antimicrobials tested: piperacillin, ticarcillin, piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, amikacin, and colistin. Multiresistance was defined according to criteria described elsewhere previously (36).

The production of transferable class B carbapenemases (metallo-β-lactamases [MBLs]) was investigated by phenotypic (Etest MBL) and genotypic (PCR and sequencing) testing (23). Additionally, the prevalence of classical chromosomal (mutational) resistance mechanisms was recently analyzed with a sample of 190 isolates from this cohort (7). In order to determine clonal relatedness, chromosomal DNAs from these 190 isolates were processed for analysis by pulsed-field gel electrophoresis (PFGE) (42).

Statistical analysis. The initially required sample size (560 samples) was calculated based on the results of a retrospective study (40), in order to detect a risk ratio (RR) between carbapenem resistance and mortality of at least 1.4, with α and β probabilities of 5% and 20%, respectively; a carbapenem-susceptible *P. aeruginosa* bacteremia (nonexposed group) mortality rate of 35%; and an expected CRPA/carbapenem-susceptible *P. aeruginosa* (CSPA) ratio of 1 to 3. The analysis performed after having exceeded the number of patients required showed a smaller difference in the effect than expected; therefore, the recruitment of patients was stopped due to logistical difficulties in achieving the recalculated sample size (1,644 patients).

The nosocomial incidence rate of *P. aeruginosa* bacteremia was adjusted by the number of stays and is expressed as the rate per 100,000 patient-days. Incidence estimations and confidence intervals (CIs) were calculated with the exact (Poisson) method. As no population census data were available, population incidence rates were not calculated.

Survival curves were constructed by means of the Kaplan-Meier method, and the log rank test was used for comparisons between groups.

Cox hazard regression was used to estimate the most unbiased measure of the effect of resistance (exposure) on the time to mortality (outcome) (24). The outcome evaluated was death, the patient admission was the unit of analysis, and the date of collection of the initial *P. aeruginosa* isolate was considered to be time zero. Cases were censored on day 30; those lost to follow-up were censored on the last follow-up day that they were known to be alive. As the final model did not satisfy the proportional hazard assumptions, the variables resistance and Pitt index were modeled as time-dependent variables. Thus, the final model was a nonproportional hazard model, in which time-dependent variables had different effects depending on the time point considered (14).

To assess effect modifications, possible interaction terms between the exposure variable (resistance) and covariates were examined and maintained in the model depending on the results of the significance test ($P < 0.05$). To control for confounding, variables were first screened to meet three classical criteria (38). In the crude analysis, variables that were associated ($P < 0.20$) with exposure (resistance), those that were associated ($P < 0.20$) with the outcome (mortality), and those that were not considered to be an intermediate variable between resistance and mortality were candidates for multivariate analysis. Variables and subsets of variables which led to substantial confounding if removed (10% change or more in the coefficient estimate) were maintained in the model, together with exposure (resistance). Results of the final model were expressed as the adjusted hazard ratio (aHR) for carbapenem resistance given different values of the interaction variables at different time points. All statistical tests were two tailed; a P value of ≤0.05 was considered significant. All statistical analyses were performed with the SPSS package, version 15.0.

RESULTS

A total of 638 episodes of *P. aeruginosa* bacteremia from 10 participating centers were entered into the study. Six episodes were excluded: three episodes with patients younger than 18 years of age, one episode that did not have complete information, one episode with a blood specimen that was obtained only through a vascular catheter without signs or symptoms of infection, and one remaining episode that was finally identified as polymicrobial bacteremia in the reference laboratory. Therefore, 632 episodes were available for evaluation, 487 (77%) CSPA and 145 (23%) CRPA episodes. In addition, nine patients were lost to follow-up: seven patients with CSPA and two with CRPA bacteremias. Epidemiological and clinical characteristics of the cohort are shown in Table

TABLE 1 Epidemiological and clinical characteristics of the 632 episodes of *P. aeruginosa* bacteremia

Variable[a]	*n*	%
Median age (yr) (IQR)	68 (55.5–77.5)	
No. of male patients	433	69
Carbapenem resistance	145	23
Type of acquisition		
Nosocomial	362	57
Community	33	5
Health care	237	38
ICU admission	145	23
Mean SAPS II (SD)	42.60 (17.9)	
Median Charlson index (IQR)	2 (1–4)	
Underlying condition	534	85
Solid malignancy	178	28
Diabetes	164	26
Immunosuppression	157	25
Heart disease	115	18
Chronic renal failure	100	16
Hematologic malignancy	93	15
Chronic lung disease	94	15
Neutropenia	67	11
Chronic neurologic disease	43	7
Cirrhosis	34	5
AIDS	7	1
High-risk/low-risk bacteremia	341/291	54/46
Origin of bacteremia		
Urinary tract	170	27
Unknown	170	27
Vascular catheter	121	19
Respiratory tract	73	12
Intra-abdominal	64	10
Soft tissue	20	3
Other	14	2
Clinical presentation of:		
Pitt score of ≥2	271	43
Initial shock/MODS	160	25
Shock/MODS at 48 h	135	21
Antibiotic therapy		
Empirical	582	92
Adequate empirical	396	68
Additional	199	31.5
Outcome		
30-day mortality	183	29
48-h mortality	64	10

[a] IQR, interquartile range.

1. A recurrence of *P. aeruginosa* bacteremia within 14 days after the initial episode occurred in 3 episodes of CSPA infection; the 3 pairs of initial and subsequent *P. aeruginosa* strains isolated from the same patients were found to be clonally identical and showed identical susceptibility patterns.

The numbers of *P. aeruginosa* episodes in each hospital are shown in Fig. 1. Among the nosocomial episodes, the median incidence density of *P. aeruginosa* bacteremia was 7.9 episodes per 100,000 patient-days (95% CI, 7.1 to 8.8), and that of CRPA bacteremia was 2.3 episodes per 100,000 patient-days (95% CI, 1.9 to 2.8).

Microbiology results. A total of 23% of the isolates were nonsusceptible to imipenem, 21.5% were nonsusceptible to meropenem, and 21% were resistant to both carbapenems. Just under one-fifth (19.6%) of the isolates met the established criteria for multiresistance (36); only amikacin (96.9%) and colistin (100%) showed conserved activity in most of the isolates.

Six of the isolates (1%), from four different hospitals, were found to produce MBLs (5 VIM-2 isolates and 1 VIM-20 isolate). In contrast, an analysis of a subset of 190 isolates from the collection revealed a high prevalence of chromosomal resistance mechanisms: up to 39% of the isolates overexpressed the β-lactamase AmpC or one of the major multidrug efflux pumps, and all tested imipenem-resistant isolates were deficient in the carbapenem porin OprD (7).

PFGE analysis showed a notable clonal diversity, with up to 152 different genotypes detected among the isolates investigated. Nevertheless, a significant clonal dissemination of multiresistant isolates was also shown: among 35 multiresistant *P. aeruginosa* isolates studied, one genotype prevailed (20/35 isolates [57%]), which was found mainly in hospitals in Catalonia (18/20 [90%]).

Patient characteristics according to carbapenem susceptibility. The demographic and clinical characteristics of patients with *P. aeruginosa* bacteremia according to carbapenem susceptibility are shown in Table 2. Among the 145 patients with CRPA bacteremias, acquisition was mainly nosocomial; they were more frequent in ICU patients (40% versus 23% [$P < 0.001$]), and the median number of days between hospital admission and the bacteremia episode was significantly higher for these patients than for patients with CSPA infections. Patients in the CSPA group were more likely than those in the CRPA group to have bacteremia from a high-risk source (272 [56%] CSPA patients versus 69 [48%] CRPA patients [$P = 0.08$]).

Mortality. The 30-day mortality cumulative incidence rates

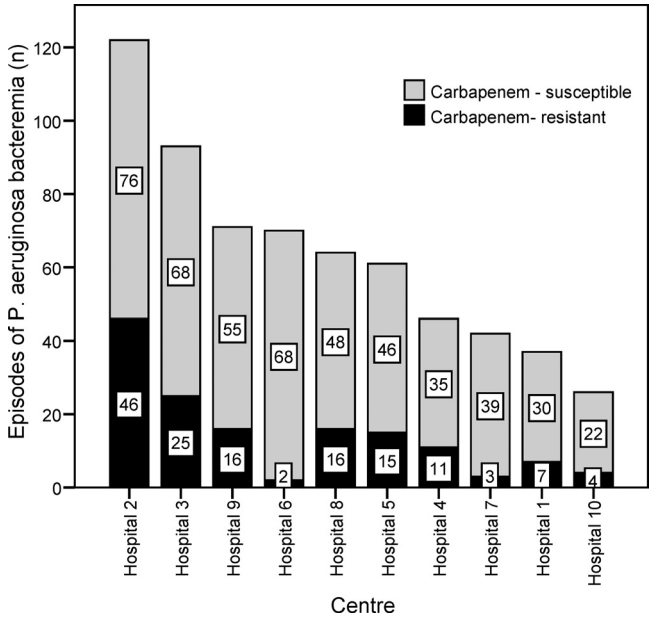
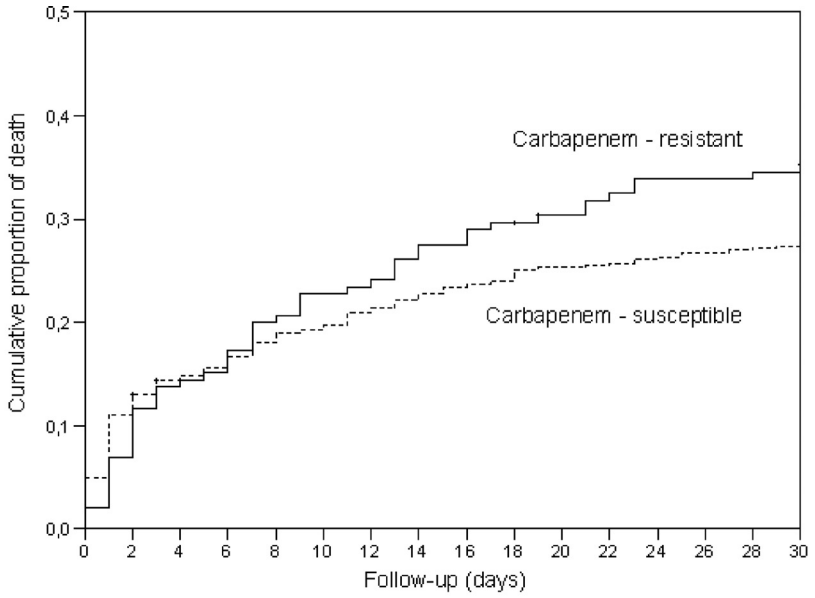


FIG 1 Episodes of bacteremia due to *P. aeruginosa* at participating hospitals.

TABLE 2 Baseline characteristics of patients with carbapenem-susceptible and carbapenem-resistant *P. aeruginosa* bacteremias

Characteristic[a]	Value for group		RR	95% CI	*P*
	CSPA ($n = 487$ [77%])	CRPA ($n = 145$ [23%])			
Median age (yr) (IQR)	68.5 (56–79)	67.5 (57–76)			0.48
No. (%) of male patients	322 (66)	111 (77)	1.44	1.05–1.99	0.018
No. (%) with nosocomial/health care acquisition	454 (93)	145 (100)	1.07	1.05–1.1	<0.001
Median no. of days from admission until bacteremia (IQR)	16 (7–28)	23.5 (13.5–43)			<0.001
No. (%) with ICU stay	112 (23)	58 (40)	1.7	1.3–2.2	<0.001
Mean SAPS (SD)	42 (32–54)	39 (25–56)			0.71
Median Charlson index (IQR)	3 (1–4)				0.23
No. (%) with underlying condition					
Any	410 (84)	124 (85.5)	1.1	0.7–1.7	0.69
Solid malignancy	14	33	0.76	0.5–1.1	0.10
Diabetes	128	36	0.9	0.7–1.3	0.73
Immunosuppressive therapy	109	48	1.5	1.1–2.0	0.009
Cardiopathy	86	29	1.1	0.8–1.7	0.52
Chronic renal failure	73	27	1.2	0.8–1.9	0.29
Hematologic malignancy	73	20	0.9	0.6–1.5	0.72
Neurologic disease	33	10	1.0	0.5–2.0	0.96
Neutropenia	54	13	0.8	0.5–1.4	0.5
Cirrhosis	22	12	1.8	0.9–3.6	0.08
AIDS	5	2	1.3	0.3–6.9	0.66
No. (%) with origin of bacteremia					
High risk	272 (56)	69 (48)	0.9	0.7–1.0	0.08
Urinary tract	126	44	1.2	0.9–1.6	0.29
Vascular catheter	89	32	1.2	0.8–1.7	0.3
Unknown	140	30	0.7	0.5–1.0	0.05
Respiratory tract	52	21	1.4	0.8–2.2	0.21
Abdominal/biliar	52	12	0.8	0.4–1.4	0.4
Soft tissue	16	4	0.8	0.3–2.5	0.75
Other	12	2	0.6	0.2–2.2	0.44
No. (%) with clinical presentation of:					
Pitt score of ≥2	200 (41)	71 (49)	1.2	1.0–1.4	0.09
Initial shock/MODS	115 (24)	45 (31)	1.3	1.0–1.8	0.07
Shock/MODS at 48 h	95 (20)	40 (28)	1.4	1.0–1.9	0.04
No. (%) on antimicrobial empirical therapy	445 (91)	137 (94.5)	1.0	1.0–1.1	0.22
No. (%) with type of empirical treatment of:					
Carbapenems	94 (19)	52 (36)	1.9	1.4–2.5	<0.001
Fluoroquinolones	59 (12)	12 (8)	0.7	0.4–1.2	0.20
Piperacillin-tazobactam	134 (28)	42 (29)	1.1	0.8–1.4	0.73
Antipseudomonal cephalosporins	110 (20.5)	26 (18)	0.9	0.8–1.0	0.23
Aminoglycosides	71 (15)	38 (26)	1.8	1.3–2.5	0.001
Colistin	6 (1)	6 (4)	3.4	1.1–10.3	0.04
No. (%) with adequate empirical therapy	338 (76)	58 (42)	0.6	0.5–0.7	<0.001
No. (%) with adequate therapy[b]	438 (94)	131 (94)	1	1–1	1
No. (%) with delay of adequate treatment of <24 h	286 (65)	52 (40)	0.6	0.5–0.8	<0.001
No. (%) with additional therapy	142 (29)	57 (39)	1.3	1.1–1.7	0.021
No. (%) with outcome of:					
30-day mortality	132 (27)	51 (35)	1.3	1.0–1.7	0.06
48-h mortality	63 (13)	17 (12)	0.9	0.5–1.5	0.70

[a] IQR, interquartile range.
[b] Adequate empirical and/or definitive treatment (excluding 24 patients who did not receive either empirical or definitive treatment).



No. at risk per day	day 0	day 1	day 2	day 6	day 20	day 30
Resistant	145	142	135	123	99	93
Susceptible	487	459	428	404	358	349

FIG 2 Kaplan-Meier survival curves of carbapenem-resistant and carbapenem-susceptible *P. aeruginosa* bacteremias ($P = 0.10$ by log rank test).

were 27% for the CSPA group (132 of 487 patients) and 35% for the CRPA group (51 of 145 patients). Figure 2 shows the 30-day survival curves and a comparison between the groups ($P = 0.10$). Although the mortality rates were similar for the groups at the end of the first 72 h (63 [13%] patients in the CSPA group died, versus 17 [12%] in the CRPA group [$P = 0.7$]), the Kaplan-Meier survival curves (Fig. 2) showed a higher mortality rate for the CSPA group in the first 2 days than for the CRPA group (12% versus 7% [the *P* value was not significant]).

The unadjusted analyses of the association of the cohort characteristics with mortality are shown in Table 3. The results of the crude analysis showed that carbapenem resistance did not have a significant impact on mortality (HR, 1.3; 95% CI, 0.9 to 1.8; $P = 0.11$). An adjusted analysis with Cox regression controlled for the source of bacteremia (high/low risk), the Pitt index, and a delay of less than 24 h to receive adequate antimicrobial therapy showed a significant interaction between carbapenem resistance and the Charlson index (Table 4). At all time points considered, the highest risk of mortality associated with carbapenem resistance was observed for the patients with the lowest Charlson index scores. The risk fell steadily as the number of comorbidities rose.

Carbapenem resistance significantly increased the risk of mortality from the fifth day after the onset of bacteremia (data not shown). However, this association was found to be not significant during the first 4 days, independent of the Charlson value.

DISCUSSION

The incidence of carbapenem resistance in *P. aeruginosa* strains has increased in recent years due to the growing resistance of this organism to antibiotics. This increase has been reported all over the world, although there are regional differences in rates (39). In fact, the nosocomial rates of carbapenem resistance in our study show a strong geographical variation inside Spain. Differences in antimicrobial consumption or epidemiological features in particular areas may contribute to these differences, although molecular analysis suggests that to some extent, the cross-transmission of carbapenem-resistant strains in the hospital and even in the interhospital setting may be responsible.

This report is the largest prospective cohort study to include a detailed clinical investigation of the impact of carbapenem resistance on mortality in patients with *P. aeruginosa* bacteremia. Our data show that carbapenem resistance was associated with significantly increased 30-day mortality rates but that the relationship depended on the degree of severity of the underlying disease (19, 30). In fact, our study describes an interaction between carbapenem resistance and underlying conditions, with an impact on mortality that is significantly higher for less severely ill patients.

In spite of the belief that infections caused by antibiotic-resistant organisms result in higher mortality rates, the studies that have evaluated this problem have produced conflicting results. There are many possible reasons for these discrepancies, since the data are highly dependent on the methods used (6). The differences observed may result, in part, from limitations in the design of retrospective studies (2, 9, 25, 26, 28, 40, 41), usually performed to identify the predictors of mortality (2, 25, 26, 28, 40, 41), and an inability to properly control for illness severity and underlying disease (16). Another potential confounder is the different pathogenic potentials of the causative pathogens under study (5, 27, 33). In addition, the types of infection, particularly those with poor prognoses, may differ or may not be balanced between the groups being compared (6). Finally, many studies had smaller numbers of patients with *P. aeruginosa* infection, thereby decreasing their statistical power.

TABLE 3 Crude analysis of effects of carbapenem resistance and other variables on mortality

Covariate[a]	Value for group		HR[b]	95% CI	*P*
	Censored	Died			
Total no. (%)	449 (71)	183 (29)			
No. (%) with carbapenem resistance	94 (21)	51 (28)	1.3	0.9–1.8	0.11
Median age (yr) (range)	65.5 (54.5–76.5)	71.5 (60.5–79.5)	1.1	1.0–1.0	0.002
No. (%) of male patients	311 (69)	122 (67)	1.1	0.8–1.5	0.60
No. (%) with nosocomial/health care acquisition	424 (94)	175 (96)	1.1	0.5–2.2	0.80
Median Charlson index (IQR)	2 (1–4)	3 (2–5)	1.1	1.1–1.2	<0.001
No. (%) with high-risk bacteremia	207 (46)	134 (73)	2.7	2.0–3.8	<0.001
No. (%) with origin of bacteremia					
Urinary tract	142 (32)	28 (15)	0.4	0.3–0.7	<0.001
Vascular catheter	100 (22)	21 (11)	0.5	0.3–0.8	0.002
Unknown	99 (22)	71 (39)	2.0	1.5–2.7	<0.001
Respiratory tract	34 (7.5)	39 (21)	2.5	1.8–3.6	<0.001
Abdominal/biliar	54 (12)	10 (5.5)	0.5	0.2–0.9	0.02
Soft tissue	11 (2.5)	9 (5.5)	1.6	0.8–3.1	0.17
Other	9 (2)	5 (3)	1.3	0.5–3.1	0.60
No. (%) with clinical presentation of:					
Pitt score of ≥2	139 (30)	132 (72)	4.5	3.3–6.3	<0.001
Initial shock/MODS	68 (15)	92 (50)	4.2	3.1–5.6	<0.001
Shock/MODS at 48 h	38 (9)	97 (56)	7.7	5.7–10.4	<0.001
No. (%) with adequate empirical antimicrobial therapy	290 (70)	106 (64)	0.8	0.6–1.1	0.19
No. (%) with delay of adequate treatment of <24 h	241 (57)	97 (67)	1.5	1.1–2.1	0.02
No. (%) with additional therapy	166 (37)	33 (18)	0.4	0.3–0.6	<0.001

[a] IQR, interquartile range.
[b] HR, hazard ratio.

Few studies have quantified the direct impact of antibiotic resistance (9, 31, 32). Carmeli et al. (9) showed previously that resistance to *P. aeruginosa* was not associated with increased mortality. In another study (31), despite the increases in the proportion of resistant organisms observed, no significant differences were found for the relative risk of death due to a resistant phenotype of the target pathogen. Finally, a recent cohort study (32) showed that the additional effect of antimicrobial resistance on mortality related to health care-associated infections was comparatively low.

TABLE 4 Adjusted[a] effect of carbapenem resistance on mortality[b]

Day	Charlson index	aHR[c]	95% CI	*P*
2	0	1.7	0.8–3.3	0.16
	1	1.5	0.8–3.0	0.24
	2	1.1	0.6–1.9	0.83
	3	0.8	0.5–1.6	0.67
	4	0.6	0.3–1.0	0.55
	5	0.6	0.3–1.1	0.09
7	0	2.2	1.2–4.1	0.01
	1	2.0	1.1–3.8	0.01
	2	1.4	0.9–2.3	0.12
	3	1.3	0.8–2.1	0.36
	4	0.8	0.5–1.3	0.31
	5	0.7	0.4–1.3	0.31
30	0	9.9	3.3–29.4	<0.001
	1	8.7	2.9–26.2	<0.001
	2	5.8	2.0–16.4	0.001
	3	6.7	1.8–24.3	0.004
	4	3.5	1.1–11.0	0.04
	5	2.6	0.8–8.0	0.1

[a] Adjusted by the source of bacteremia (high risk/low risk), the Pitt score, and a delay of less than 24 h to receive adequate antibiotic therapy.
[b] Shown is the interaction between carbapenem susceptibility and the Charlson index at different time points.
[c] aHR, adjusted hazard ratio.

Patients with a greater severity of underlying disease may have many reasons for increased mortality, and the addition of bacteremia due to antimicrobial resistance to their life-threatening problems may be inconsequential. Thus, it is essential to select an adequate methodology (6, 17, 29) and adjust for the severity of the illness and comorbidities before infection, as these factors can have a significant effect on the measurement of outcomes. We feel that we used the best methodology available to us; certain research questions can be answered only by use of observational studies, due to obvious ethical constraints. By using a predetermined uniform endpoint of mortality at 30 days, we avoided the potential bias in the assignment of a cause of death, which is particularly problematic for patients with many comorbid conditions. Regarding the type of infection, microbiologically documented bacteremia represents the optimal model for investigating the pathogenic significance of resistance. Finally, we used a standardized underlying disease index, the Charlson comorbidity score, a valid method for estimating the risk of death from comorbid disease, and we measured comorbidities before the development of bacteremia.

Finally, our study suggests that the increase in mortality explained by carbapenem resistance is not evident during the first days after the onset of bacteremia, as a recent single-center study indicated (40). These findings may be consistent with *in vitro* ev-

idence showing that resistance genes or mutations can alter the fitness of microorganisms (4), making them less virulent and reducing their capacity to generate deleterious host inflammatory responses (22). Nevertheless, the complex interplay between resistance mechanisms, cost-compensatory mutations, fitness, and virulence in the clinical setting has yet to be fully elucidated (1).

The present investigation may have limitations. Unfortunately, because of the lack of statistical power to detect true but small differences, the inferences that can be made from our data may be limited despite the large sample size. In addition, a system to score the severity of acute illness, which is well validated for predicting bacteremia prognoses (11), was assessed at the time of bacteremia presentation. If the severity of the illness was an intermediate variable in the causal pathway between carbapenem resistance and mortality, adjustment by that variable could have led to an underestimation of the magnitude of the effect (16); however, no such association was demonstrated. In our opinion, this multi-institutional study reflects a broad spectrum of patients, and given the fact that we derived our cohort from a multicenter study, we believe that these results are applicable to other settings.

In conclusion, to our knowledge, this is the first prospective multicenter study to investigate the adjusted impact of antimicrobial resistance on the mortality of *P. aeruginosa* bloodstream infections. We have documented the distribution of this epidemiological problem in Spain. The hospitals studied showed marked diversity in the occurrence of these strains, and this heterogeneity is due, at least in part, to clonal dissemination. The study clarifies the relationship between carbapenem-resistant *P. aeruginosa* bacteremia and mortality, although the impact was observed mainly for patients with a lower severity of underlying disease. The lesser effect of resistance during the first days after the onset of bacteremia may have implications for the design of empirical antibiotic strategies. Better risk scores should be developed to distinguish patients at a low risk of mortality due to infections with antimicrobial-resistant pathogens from those for whom the broadest-spectrum therapy could be truly beneficial.

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