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Mortality Attributable to Bloodstream Infections Caused by Different Carbapenem-Resistant Gram-Negative Bacilli: Results From a Nationwide Study in Italy (ALARICO Network)

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Background. Our aim was to analyze mortality attributable to carbapenem-resistant (CR) gram-negative bacilli (GNB) in patients with bloodstream infections (BSIs).

Methods. Prospective multicentric study including patients with GNB-BSI from 19 Italian hospitals (June 2018–January 2020). Patients were followed-up to 30 days. Primary outcomes were 30-day mortality and attributable mortality. Attributable mortality was calculated in the following groups: *Klebsiella pneumoniae* carbapenemase (KPC)–producing Enterobacterales, metallo-β-lactamases (MBL)–producing Enterobacterales, CR-*Pseudomonas aeruginosa* (CRPA), CR-*Acinetobacter baumannii* (CRAB). A multivariable analysis with hospital fixed-effect was built to identify factors associated with 30-day mortality. Adjusted OR (aORs) were reported. Attributable mortality was calculated according to the DRIVE-AB Consortium.

Results. Overall, 1276 patients with monomicrobial GNB BSI were included: 723/1276 (56.7%) carbapenem-susceptible (CS)-GNB, 304/1276 (23.8%) KPC-, 77/1276 (6%) MBL-producing CRE, 61/1276 (4.8%) CRPA, and 111/1276 (8.7%) CRAB BSI. Thirty-day mortality in patients with CS-GNB BSI was 13.7% compared to 26.6%, 36.4%, 32.8% and 43.2% in patients with BSI by KPC-CRE, MBL-CRE, CRPA and CRAB, respectively ($P < .001$). On multivariable analysis, age, ward of hospitalization, SOFA score, and Charlson Index were factors associated with 30-day mortality, while urinary source of infection and early appropriate therapy resulted protective factors. Compared to CS-GNB, MBL-producing CRE (aOR 5.86, 95% CI 2.72–12.76), CRPA (aOR 1.99, 95% CI 1.48–5.95) and CRAB (aOR 2.65, 95% CI 1.52–4.61) were significantly associated with 30-day mortality. Attributable mortality rates were 5% for KPC-, 35% for MBL, 19% for CRPA, and 16% for CRAB.

Conclusions. In patients with BSIs, carbapenem-resistance is associated with an excess of mortality, with MBL-producing CRE carrying the highest risk of death.

Keywords. attributable mortality; *Klebsiella pneumoniae*; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; carbapenem resistance.

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Carbapenem-resistant (CR) gram-negative bacilli (GNB) represent a leading global threat of this century. The 2017 World Health Organization (WHO) global priority list of pathogens ranked CR Enterobacterales (CRE), CR *Pseudomonas aeruginosa* (CRPA), and CR *Acinetobacter baumannii* (CRAB) in the highest priority category to incentivize research and development of new antibiotics [1-3]. Bloodstream infections (BSIs) accounted for more than 70% of deaths attributable to antimicrobial resistance (AMR) in 2019 [4]. Deaths attributable to CRE infections vary from 20% to 45% [5-7], while studies that included patients with infections caused by CRAB reported mortality rates as high as 70% [8-11]. However, the attributable mortality estimation is usually based on epidemiological data that do not take into account clinical variables. The knowledge of mortality attributable to infections caused by specific resistant organisms is important to highlight the magnitude of AMR in a clinical context and to emphasize the need for resource prioritization and multifaceted actions of prevention.

Our objective was to analyze mortality attributable to CR GNB in patients with BSIs from a national multicentric cohort.

METHODS

Study Design

This was a prospective study that included patients with BSIs caused by GNB in 19 hospitals belonging to the Advancing knowLedge on Antimicrobial Resistant Infections COllaboration (ALARICO) Network (June 2018–January 2020), a group of Italian hospitals (Supplementary Figure 1) aimed to promote epidemiological and clinical studies on multidrug-resistant (MDR) infections.

BSI episodes were categorized into 5 categories according to the causative pathogen: carbapenem-susceptible (CS) GNB; *Klebsiella pneumoniae* carbapenemase (KPC)–producing CRE; metallo-β-lactamases (MBL)–producing CRE; CRPA; and CRAB. Patients with polymicrobial BSIs caused by GNB plus gram-positive bacteria or fungi and those caused by more than 1 GNB (mixed GNB BSI) were excluded. Day 1 was defined as the day of index blood culture collection. Patients were followed up until 30 days from day 1. Thirty-day mortality was defined as death that occurred within 30 days from day 1 and ascertained by dedicated subinvestigators at each participating center. Patients discharged before completion of follow-up underwent were contacted by telephone to collect data about outcome.

The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The study was approved by the internal review board of the promoter center and by local ethical committees of participating centers. Written informed consent was obtained from study participants. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplementary Materials, Supplementary Table 1).

Outcomes

The study outcome was the mortality rate for patients with BSIs caused by different categories of CR GNB (KPC-producing CRE, MBL-producing CRE, CRPA, and CRAB) compared with that of patients with CS GNB bacteremia. The primary outcome measures were 30-day mortality and attributable mortality.

Study Population and Data Collection

Adults (aged >18 years) admitted to a participating center with a BSI, defined according to the Centers for Disease Control and Prevention/National Healthcare Safety Network criteria [12], were included. A central venous catheter (CVC) was considered a source of infection if the differential time to positivity between blood cultures drawn through the CVC and a peripheral vein was ≥120 minutes [13]. Control of a removable source of infection was defined as removal of any preexisting contaminated CVC and as drainage of intraabdominal abscesses or other fluid collections thought to be the source of infection [14]. BSI episodes were classified as hospital- or community-acquired, as previously described [15]. The Sequential Organ Failure Assessment (SOFA) score and Pitt bacteremia score at the onset of BSI were calculated [16, 17].

Data were collected with a preformed clinical report form (CRF) using Castor EDC [18]. All cases were deidentified. The data manager performed periodic quality control by reviewing completed forms for completeness and consistency for each site. The CRF included demographics, comorbidities, clinical characteristics at BSI onset, microbiological data, and outcome.

Microbiological Methods

Isolate identification was performed using matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI Biotyper, Bruker Daltonics) or automated systems according to the technology available at each center. Antimicrobial susceptibility tests were performed with the Tecan automated system (Tecan Trading AG, Switzerland), SensititreTM EUMDROXF (Thermo Fisher Scientific, Waltham, MA), Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France), or MicroScan system (Beckman Coulter, Brea, CA) according to the manufacturer's instructions. The presence of a bla gene, including bla_{KPC}, bla_{NDM}, bla_{VIM}, and bla_{OXA-48}, among CRE isolates was determined with polymerase chain reaction assay using the GeneXpert System (Cepheid) as previously reported [19]. GeneXpert testing for detection of carbapenemase genes was performed at the local microbiology laboratories with CRE isolates. Minimum inhibitory concentrations (MICs) were classified according to

breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST v.13) [20].

CRE were defined as Enterobacterales isolates resistant to any of the carbapenems (MIC >8 μg/mL for meropenem, >4 μg/mL for imipenem, >0.5 μg/mL for ertapenem) or harboring a gene encoding a carbapenemase [20]. For Enterobacterales that exhibit intrinsic imipenem nonsusceptibility (*Morganella morganii*, *Proteus*, *Providencia* species), resistance to carbapenems other than imipenem was required [21]. CRPA and CRAB were isolates resistant to meropenem (>8 μg/mL) or imipenem (>4 μg/mL).

Statistical Analyses

Continuous variables were reported as median with interquartile ranges and categorical variables as numbers and percentages. Continuous variables were compared using the Student *t*-test and Mann–Whitney *U* test as appropriate. Analysis of variance was used to analyze the differences of continuous variables among multiple groups. Categorical variables were evaluated using the χ^2 or 2-tailed Fisher exact test, as appropriate.

A multivariable regression analysis was performed to identify factors independently associated with 30-day mortality. Variables with statistical significance in the univariate analysis ($P < .05$) were entered into the multivariable model. Only variables present at the onset of BSI were included. Septic shock (which may be on the causal pathway from lack of early appropriate therapy) and source control (which represents an intervention and may be a function of whether a patient was clinically stable enough for a procedure, so that lack of source control may be on the causal pathway from disease severity) were not included. The Charlson comorbidity index was used as a surrogate of comorbidities and included instead of each single underlying disease. SOFA score (and not Pitt score) was used as a tool for disease severity. The variance inflation factor (VIF) value was calculated to control the influence of collinearity. We assumed a lack of multicollinearity if all variables had a VIF value <2. No collinearity was detected among included variables (Supplementary Table 2). Thus, adjustment variables included in the model were ward of hospitalization, SOFA score, Charlson comorbidity index, radiotherapy or chemotherapy, type of acquisition (community-acquired as the reference variable), urinary tract as the source of infection, early appropriate therapy (defined as in vitro active therapy administered within 24 hours from blood culture collection), age, male sex, and type of pathogen (CS GNB as the reference). A fixed-effects Firth bias-reduced penalized-likelihood logistic regression model with hospital-specific intercepts was performed to account for differences across centers. Cases with at least 1 variable with more than 50% missing were excluded. Imputation for missing variables was considered if missing values were less than 20%. We initially performed multiple imputation, generating 5 different completed datasets based on sampling from their full conditional distributions through a Markov chain Monte Carlo algorithm. For sensitivity analysis, we compared the 5 regression results, the pooled analysis, the complete case analysis after list-wise exclusion, and hot-deck single imputation. Due to the very low fraction of missing values, all of these analyses have only minimal differences. Adjusted survival curves were estimated using inverse probability of treatment weighting (IPTW) [22].

Attributable mortality was calculated for each cohort of CR GNB (KPC-producing CRE, MBL-producing CRE, CRPA, and CRAB) compared with the cohort of patients with CS GNB BSI. Attributable mortality was calculated, as described by the Driving re-investment in research and development and responsible antibiotic use (DRIVE-AB) Consortium [23], with the following formula: $(P_0[\text{mortality in controls}] \times [\text{aOR } \{\text{adjusted odds ratio}\} - 1] \times [1 - P_0])/(\text{aOR} \times P_0 + [1 - P_0])$, where P_0 was the mortality proportions for the control group and aOR was the adjusted odds ratios for 30-day mortality. aORs from the multivariable regression model were used to calculate the attributable mortality.

Subgroup analyses were performed to reduce the risk of heterogeneity. Attributable mortality rates were calculated in the group of patients with BSIs caused by Enterobacterales (KPC-producing CRE vs CS Enterobacterales and MBL-producing CRE vs CS Enterobacterales) and in patients with BSIs caused by CRPA vs CSPA. Subgroup analysis was not performed in patients with *A. baumannii* BSI because only 8 strains were CS. The above-described selection method for the multivariable analysis was used for all models in the study.

Statistical significance was established at $P \leq .05$. All reported *P* values are 2-tailed. The results obtained were analyzed using commercially available statistical software packages (IBM SPSS version 27, Armonk, NY; R version 4.1.2).

RESULTS

Study Population

During the study period, 1469 cases of GNB BSI were identified. However, 184 patients were excluded: 83 (5.6%) had polymicrobial BSI, 18 (1.2%) had a mixed GNB BSI, 60 (4.1%) had more than 50% missing data, 14 (0.9%) received a "do not resuscitate order," and 9 (0.6%) did not provide informed consent. Among the remaining 1285 BSIs, 9 episodes caused by OXA-48–producing CRE were excluded due to the limited number of cases. The final cohort comprised 1276 patients (see the study flowchart in Figure 1).

Overall, 723 of 1276 (56.7%) patients had a BSI caused by CS GNB, while 553 of 1276 (43.3%) had a CR GNB BSI. Patients with CR GNB included 304 (23.8%) KPC-producing CRE, 77 (6%) MBL-producing CRE (7 verona integron-encoded

metallo-β-lactamase [VIM] and 70 New Delhi metallo-β-lactamase [NDM]), 61 (4.8%) CRPA, and 111 (8.7%) CRAB.

Table 1 shows the comparison between patients with CS GNB BSI and those with the different classes of CR GNB BSI. Hospital acquisition was higher for CRE (KPC, 79.3%; MBL, 77.9%), CRPA (82%), and CRAB (94.9%) compared with CS GNB (75.1%, $P < .001$). Patients with CR GNB were more commonly hospitalized in the intensive care unit (ICU) compared with CS GNB (KPC, 38.8%; MBL, 49.4%; CRPA, 57.4%; CRAB, 67.6% vs CS GNB, 19.8%; $P < .001$). Sources of BSI according to the causative pathogen are shown in Figure 2.

Primary Outcome

Overall, 30-day mortality in the whole population was 21.6% (13.7% in patients with CS vs 32% in patients with CR GNB BSIs, 95% confidence interval [CI]: 0.26–0.45; $P < .01$). Thirty-day mortality rates were 26.6%, 36.4%, 32.8%, and 43.2% in patients with BSI by KPC-producing CRE, MBL-producing CRE, CRPA, and CRAB, respectively (KPC vs CS GNB: 95% CI:1.64–3.18, $P < .001$; MBL vs CS GNB: 95% CI: 2.16–5.9, $P < .001$; CRPA vs CRPA: 95% CI: 1.73–5.45, $P < .001$; CRAB vs CS GNB: 95% CI: 3.11–7.34, $P < .001$).

A comparison of survivors and nonsurvivors is shown in Table 2. Compared with survivors, nonsurvivors were older, more frequently cared for in the ICU, were more likely to be affected by comorbidities, and more commonly had septic shock and less frequently had urinary tract as the source of infection. They also less frequently received the appropriate antibiotic therapy within 24 hours from BSI onset. On multivariable analysis (Table 3), hospitalization in the ICU (aOR, 7.09; 95% CI,: 3.28–17.22; $P < .001$) or medical wards (aOR, 5.23; 95% CI: 2.37–12.29; $P < .001$), SOFA score (aOR, 1.23; 95% CI: 1.17–1.29; $P < .001$), Charlson comorbidity index (aOR, 1.09; 95% CI: 1.03–1.16; $P = .004$), and age (aOR, 1.04; 95% CI: 1.02–1.05; $P < .001$) were factors independently associated with 30-day mortality, while urinary tract as the source of infection (aOR, 0.42; 95% CI: .27–.66; $P < .001$) and early administration of appropriate therapy (aOR, 0.62; 95% CI: .43–.89; $P = .010$) had an inverse association with the primary outcome. Among type of pathogen, MBL-producing CRE (aOR, 5.86; 95% CI: 2.72–12.76), CRPA (aOR, 1.99; 95% CI: 1.48–5.95), and CRAB (aOR, 2.65; 95% CI: 1.52–4.61) were associated with 30-day mortality.

As shown in Table 4, the lowest attributable mortality was found in patients with BSI caused by KPC-producing Enterobacterales (5%), while the highest was found in those with BSI by MBL-producing CRE (35%). Attributable mortality in patients infected by CRAB and CRPA was 16% and 19%, respectively. Figure 3 shows the timeline from admission to BSI and outcome for each group.

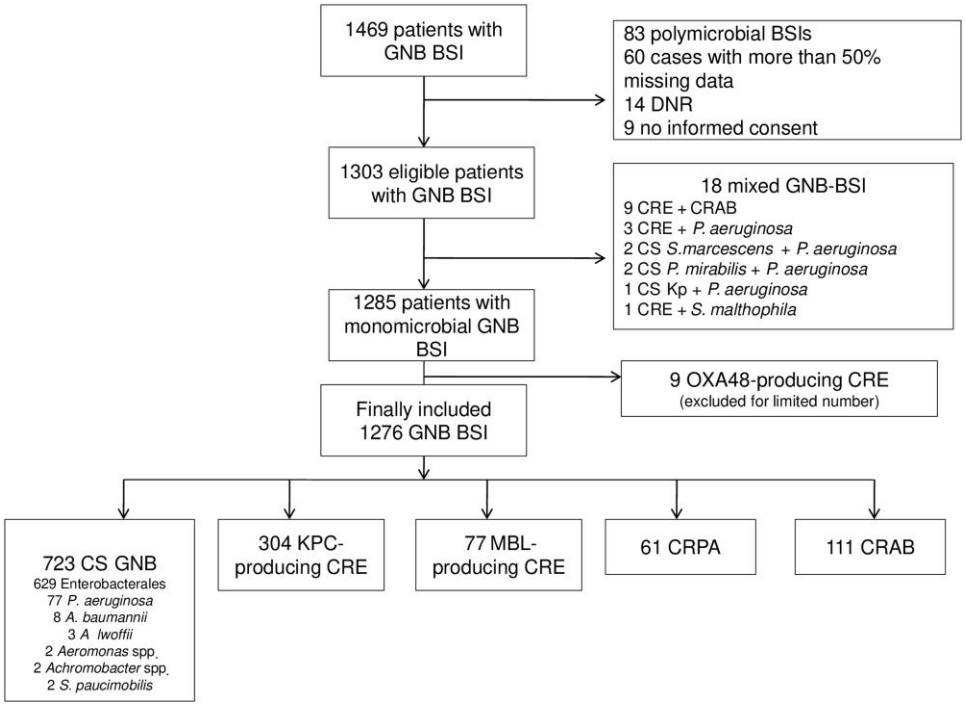


Figure 1. Study flowchart. Abbreviations: BSI, bloodstream infection; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CS, carbapenem-susceptible; DNR, do not resuscitate; GNB, gram-negative bacilli; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase.

Table 1. Comparison of Patients With Bloodstream Infections (BSI) Caused by Non–Carbapenem-Resistant Gram-Negative Bacilli and Those With BSIs Due to Different Categories of Carbapenem-Resistant Gram-Negative Bacilli

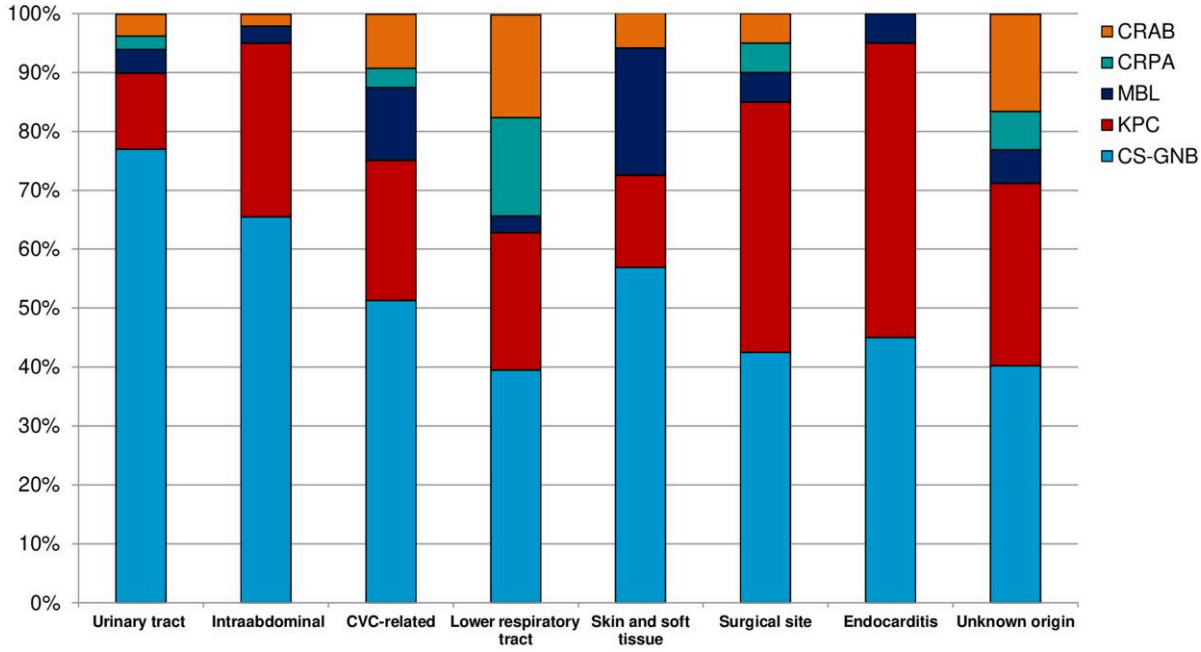
Variable	Carbapenem-Susceptible Gram-Negative Bacilli BSI N = 723 (%)	*Klebsiella pneumoniae* Carbapenemase BSI N = 304 (%)	Metallo-Beta-Lactamase BSI N = 77 (%)	Carbapenem-Resistant *Pseudomonas aeruginosa* BSI N = 61 (%)	Carbapenem-Resistant *Acinetobacter baumannii* BSI N = 111 (%)	*P* Value[a]
Age, median (IQR), y	70 (56–78)	64 (53–73)	71 (52–78)	66 (43.5–74)	68.5 (53.75–79)	<.001
Male sex	425 (58.8)	196 (64.5)	45 (58.4)	26 (42.6)	58 (52.3)	.013
Ward of hospitalization at BSI onset						<.001
Medical	478 (66.1)	155 (51)	30 (39)	14 (23)	33 (19.7)	
Surgical	102 (14.1)	31 (10.2)	9 (11.7)	12 (19.7)	3 (2.7)	
Intensive care unit	143 (19.8)	118 (38.8)	38 (49.4)	35 (57.4)	75 (67.6)	
Acquisition						<.001
Community-acquired	180 (24.9)	63 (20.7)	17 (22.1)	11 (18)	6 (5.4)	
Hospital-acquired	543 (75.1)	241 (79.3)	60 (77.9)	50 (82)	105 (94.9)	
Comorbidity						
Diabetes mellitus	210 (29)	79 (26)	26 (33.8)	30 (49.2)	31 (27.9)	.007
Cardiovascular disease	298 (41.2)	152 (28.1)	35 (45.5)	2 (3.3)	54 (48.6)	<.001
Chronic obstructive pulmonary disease	107 (14.8)	57 (18.8)	13 (16.9)	2 (3.3)	19 (17.1)	.039
Chronic renal failure	146 (20.2)	57 (18.8)	12 (15.6)	14 (23)	22 (19.8)	.823
Chronic liver disease	98 (13.6)	32 (10.6)	10 (13)	6 (9.8)	7 (6.3)	.199
Solid cancer	207 (28.6)	45 (14.8)	16 (20.8)	6 (9.8)0	6 (5.4)	<.001
Solid organ transplantation	45 (6.2)	25 (8.2)	6 (7.8)	0	2 (1.8)	.035
Charlson comorbidity index, median (IQR)	3 (2–6)	2 (1–4)	2 (0–4)	2 (1–3)	2 (1–4)	<.001
Radiotherapy or chemotherapy, last 30 d	106 (14.7)	20 (6.6)	2 (2.6)	0	3 (2.7)	<.001
Previous hospitalization, last 3 mo	304 (42)	161 (53)	42 (54.5)	18 (29.5)	39 (35.1)	<.001
Previous antibiotic therapy, last 30 d	337 (46.6)	190 (62.5)	57 (74)	33 (54.1)	77 (69.4)	<.001
Source of infection						<.001
Urinary tract	269 (37.2)	45 (14.8)	14 (18.2)	8 (13.1)	13 (17)	
Respiratory tract	66 (9.1)	39 (12.8)	5 (6.5)	28 (45.9)	29 (26.1)	
Abdomen	133 (18.4)	60 (19.7)	6 (7.8)	0	4 (3.6)	
Surgical site	17 (2.4)	17 (5.6)	2 (2.6)	2 (3.3)	2 (1.8)	
Skin and soft tissue	29 (4)	8 (2.6)	11 (14.3)	0	3 (2.7)	
Central venous catheter–related	95 (13.1)	44 (14.5)	23 (29.9)	6 (9.8)	17 (15.3)	
Endocarditis	9 (1.2)	10 (3.3)	1 (1.3)	0	0	
Unknown	105 (14.5)	81 (26.6)	15 (19.5)	17 (27.9)	43 (38.7)	
Septic shock at BSI onset	113 (15.6)	85 (28)	23 (29.9)	15 (24.6)	26 (23.4)	<.001
Sequential Organ Failure Assessment score at BSI onset, median (IQR)	3 (2–6)	4 (2–6)	3 (0.5–6)	6 (2–9)	3 (2–7)	.008
Pitt bacteremia score, median (IQR)	1 (0–3)	2 (1–5)	2 (1–4)	3 (1–4)	2 (1–6)	<.001
Source control[b]	419 (75.9)	121 (65.8)	41 (71.9)	12 (75)	29 (74.4)	.118
Early appropriate therapy	509 (70.4)	115 (37.8)	11 (14.3)	22 (36.1)	26 (23.4)	<.001
30-day mortality	99 (13.7)	81 (26.6)	28 (36.4)	20 (32.8)	48 (43.2)	<.001

Source control was defined as control of removable source of infection.

Abbreviations: BSI, bloodstream infection; IQR, interquartile range.

[a] *P* value across groups for continuous variables was calculated using analysis of variance.

[b] There were 848 of 1276 (552 carbapenem-susceptible gram-negative bacilli; 184 *Klebsiella pneumoniae* carbapenemase; 57 metallo- β-lactamase; 16 carbapenem-resistant *Pseudomonas aeruginosa*; 39 carbapenem-resistant *Acinetobacter baumannii*) patients who had a removable source of infection.



N = 1276	n = 349	n = 203	n = 185	n = 167	n = 51	n = 40	n = 20	n = 261
CS-GNB	269 (77.1%)	133 (65.5%)	95 (51.4%)	66 (39.4%)	29 (56.9%)	17 (42.5%)	9 (45%)	105 (40.2%)
KPC-E	45 (12.9%)	60 (29.5%)	44 (23.8%)	39 (23.4%)	8 (15.7%)	17 (42.5%)	10 (50%)	81 (31%)
MBL-E	14 (4%)	6 (3%)	23 (12.4%)	5 (3%)	11 (21.6%)	2 (5%)	1 (5%)	15 (5.7%)
CRPA	8 (2.3%)	0	6 (3.2%)	28 (16.8%)	0	2 (5%)	0	17 (6.5%)
CRAB	13 (3.7%)	4 (2%)	17 (9.2%)	29 (17.4%)	3 (5.8%)	2 (5%)	0	43 (16.5%)

Figure 2. Distribution of causative pathogens according to source of BSI. Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CS, carbapenem-susceptible; CVC, central venous catheter; GNB, gram-negative bacilli; KPC-E, *Klebsiella pneumoniae* carbapenemase Enterobacterales; MBL-E, metallo-β-lactamases Enterobacterales.

Survival curves adjusted for IPTW according to each type of causative GNB showed that patients with BSI caused by MBL-producing CRE had the highest risk of dying (Figure 4).

Subgroup Analysis

Subgroup analyses are reported in the Supplementary Materials. Among patients with Enterobacterales BSI (n = 1009), 30-day mortality was higher in patients infected by KPC-producing CRE (81 of 304; 26.6%; 95% CI: 1.59–3.13) and MBL-producing CRE (28 of 77; 36.4%; 95% CI: 2.09–5.87) compared with patients with BSI caused by CS Enterobacterales (88 of 628; 14%; $P < .001$). Results for multivariable analysis of factors associated with 30-day mortality are shown in Supplementary Table 3. Mortality attributable to MBL-producing Enterobacterales was 37% (aOR, 6.30; 95% CI: 2.71–15.02; Supplementary Table 4).

Of 138 patients with *P. aeruginosa* BSI, 30-day mortality was 11.7% (9 of 77) in those infected by CSPA vs 32.8% (20 of 61) in those infected by CRPA (95% CI: .11–.65; $P = .003$). Results for multivariable analysis of factors associated with 30-day mortality are shown in Supplementary Table 5. The attributable mortality of patients with BSI by CRPA was 17% (aOR, 33.12; 95% CI: .78–12.9; Supplementary Table 4).

DISCUSSION

We estimated the mortality attributable to different types of CR GNB in a multicentric cohort of patients with GNB BSIs. In this study, the attributable mortality ranged from 5% in patients with KPC- to 35% in those with MBL-producing Enterobacterales bacteremia. These findings have notable importance and novelty.

Recent epidemiological studies have highlighted the global burden of AMR but have combined heterogeneous data with different infection types and pathogens (including MDR gram-positive bacteria, GNB and *Mycobacterium tuberculosis*) [3, 4]. No clinical studies have specifically investigated the mortality attributable to different CR GNB [24]. Smaller observational studies and systematic reviews used different measures to quantify attributable mortality [7, 25, 26].

Table 2. Comparison of Patients Who Died and Those Who Did Not Die Within 30 Days From Bloodstream Infection Onset

Variable	Survivors N = 1000 (%)	Nonsurvivors N = 276 (%)	*P* Value
Age, median (IQR)	66.5 (53–76)	71 (58–81)	<.001
Male sex	606 (60.6)	144 (52.2)	.012
Ward of hospitalization at BSI onset			<.001
Medical	579 (57.9)	131 (47.5)	
Surgical	148 (14.8)	9 (3.3)	
Intensive care unit	273 (27.3)	136 (49.3)	
Acquisition			.002
Community-acquired	420 (42)	88 (31.9)	
Hospital-acquired	580 (58)	188 (68.1)	
Comorbidity			
Diabetes mellitus	273 (27.3)	103 (37.3)	.001
Cardiovascular disease	393 (39.3)	148 (53.6)	<.001
Chronic obstructive pulmonary disease	141 (14.1)	57 (20.7)	.008
Chronic renal failure	179 (17.9)	72 (26.1)	.002
Chronic liver disease	116 (11.6)	37 (13.4)	.417
Solid cancer	236 (23.6)	44 (15.9)	.007
Solid organ transplantation	64 (6.4)	14 (5.1)	.415
Charlson comorbidity index, median (IQR)	3 (1–5)	3 (2–5)	.008
Radiotherapy or chemotherapy, last 30 d	117 (11.7)	14 (5.1)	.001
Previous hospitalization, last 3 mo	444 (44.4)	120 (43.5)	.785
Previous antibiotic therapy, last 30 d	537 (53.7)	157 (22.6)	.347
Source of infection			<.001
Urinary tract	311 (31.1)	38 (13.8)	
Respiratory tract	100 (10)	67 (24.3)	
Abdomen	169 (16.9)	34 (12.3)	
Surgical site	28 (2.8)	12 (4.3)	
Skin and soft tissue	41 (4.1)	10 (19.6)	
Central venous catheter–related	163 (16.3)	22 (8)	
Endocarditis	12 (1.2)	8 (2.9)	
Unknown	176 (17.6)	85 (32.6)	
Septic shock at BSI onset	148 (14.8)	114 (41.3)	<.001
Sequential Organ Failure Assessment score at BSI onset, median (IQR)	3 (1–5)	6 (3–9)	<.001
Pitt bacteremia score, median (IQR)	1 (0–3)	3 (1.75–6)	<.001
Source control[a]	563 (77.8)	59 (47.6)	<.001
Early appropriate therapy	572 (57.2)	111 (40.2)	<.001
Type of pathogen			<.001
Carbapenem-susceptible gram-negative bacilli	624 (62.4)	99 (35.9)	
Klebsiella pneumoniae–producing GNB	223 (22.3)	81 (29.3)	
Metallo-β-lactamase–producing GNB	49 (4.9)	28 (10.1)	
Carbapenem-resistant *Pseudomonas aeruginosa*	41 (4.1)	20 (7.2)	
Carbapenem-resistant *Acinetobacter baumannii*	63 (6.3)	48 (17.4)	

Abbreviations: BSI, bloodstream infection; GNB, gram-negative bacilli; IQR, interquartile range.

[a]A total of 848 patients had a removable source of infection (724 survivors; 124 nonsurvivors).

Table 3. Multivariable Logistic Regression of Factors Independently Associated With 30-Day Mortality

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value
Ward of hospitalization		
Surgical	*reference*	
Medical	5.23 (2.37–12.29)	<.001
Intensive care unit	7.09 (3.28–17.22)	<.001
Sequential Organ Failure Assessment score at bloodstream infection onset, each point increment	1.23 (1.17–1.29)	<.001
Charlson comorbidity index, each point increment	1.09 (1.03–1.16)	.004
Radiotherapy or chemotherapy	0.66 (.33–1.26)	.208
Acquisition		
Community-acquired	*reference*	
Hospital-acquired	1.01 (.63–1.65)	.965
Source of infection		
Nonurinary tract	*reference*	
Urinary tract	0.42 (.27–.66)	<.001
Early appropriate therapy	0.62 (.43–.89)	.010
Age, each year increment	1.04 (1.02–1.05)	<.001
Sex		
Female	*reference*	
Male	0.82 (.59–1.14)	.234
Type of pathogen		
Carbapenem-susceptible gram-negative bacilli	*reference*	
Klebsiella pneumoniae–producing GNB	1.43 (.92–2.22)	.109
Metallo-β-lactamase–producing GNB	5.86 (2.72–12.76)	<.001
Carbapenem-resistant *Pseudomonas aeruginosa*	2.99 (1.48–5.95)	.002
Carbapenem-resistant *Acinetobacter baumannii*	2.65 (1.52–4.61)	.001

For binary variables, absence of the condition was the reference variable. Penalized logistic regression with center-specific fixed effects. Adjusted odds ratios have been used to calculate the attributable mortality.

Our study highlights the correlation of the WHO "priority pathogens" on the outcome of patients with BSIs. We found that carbapenem resistance is associated with an increased risk of death compared with carbapenem susceptibility in CS GNB BSI, with the highest risk of dying detected in the group of MBL-producing CRE, followed by CRPA and CRAB. This observation has specific importance considering the changing epidemiology of CRE worldwide. Although the greatest percentage of MBL-producing CRE is reported in the Asia/South Pacific and Middle East/Africa regions [27], MBL production in Enterobacterales is increasingly reported as a cause of healthcare-associated infections in Europe and the United States [28-33]. Of importance, high-risk clones (such as ST147, ST258, and ST101) have been widely implicated in the global spread of bla_{NDM} genes [19, 34]. In a previous study, patients with rectal colonization by ST147 NDM-producing

Table 4. Primary Outcome: Crude 30-Day Mortality and Attributable Mortality for Each Cohort of Carbapenem-Resistant Gram-Negative Bacilli

Carbapenam-resistant Gram negative bacilli	Crude 30-Day Mortality	Adjusted Odds Ratio of Death[a]	Attributable Mortality, Controls: Patients With Carbapenem-Susceptible Bloodstream Infection
Klebsiella pneumoniae carbapenemase–producing Enterobacterales[b]	26.5%	1.43 (0.92–2.22)	5%
Metallo-β-lactamase–producing Enterobacterales	36.4%	5.86 (2.72–12.76)	35%
Carbapenem-resistant *Pseudomonas aeruginosa*	32.8%	2.99 (1.48–5.95)	19%
Carbapenem-resistant *Acinetobacter baumannii*	43.2%	2.65 (1.52–4.61)	16%

Comparator represented by the cohort of carbapenem-susceptible gram-negative bacilli. Formula for attributable mortality: (P0 ∗(aOR − 1)∗(1 − P0))(aOR∗P0 + (1 − P0)). Decimals were rounded to the nearest unit.

[a]Adjusted odds ratio (aOR) calculated on regression analysis showed in Table 3.

[b]aOR for *Klebsiella pneumoniae* carbapenemase not statistically significant.

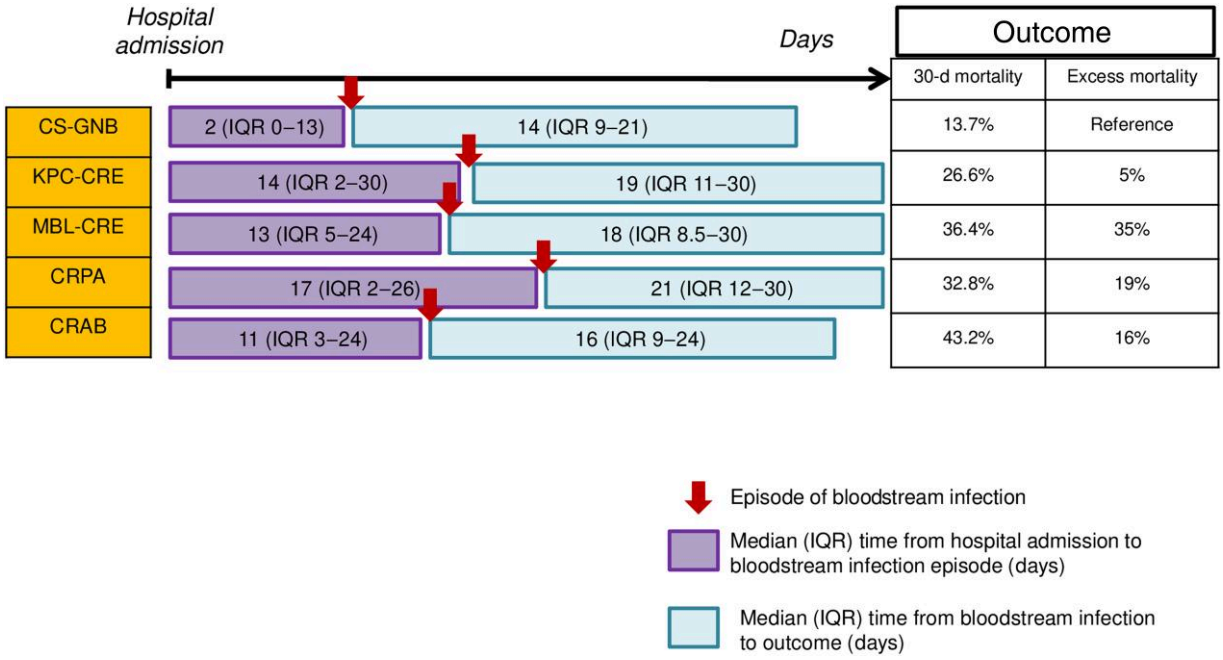
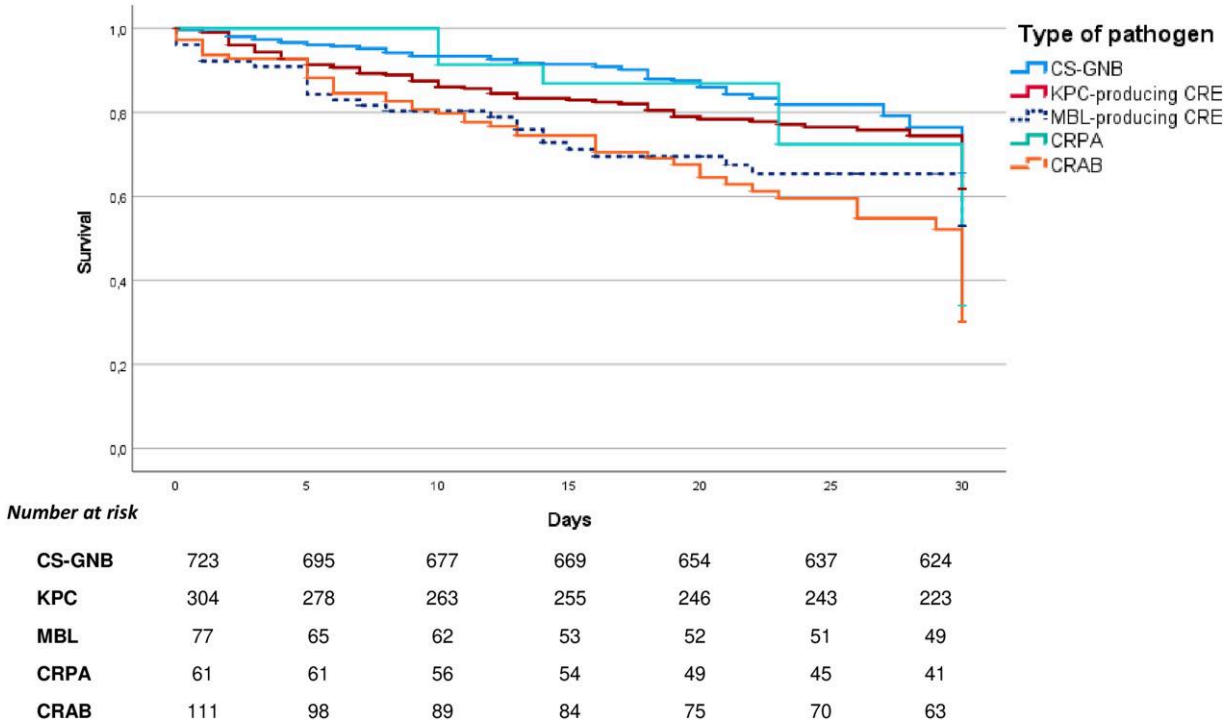


Figure 3. Study timeline of patient events in relation to the hospital admission, exposures, and outcomes. Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CS, carbapenem-susceptible; GNB, gram-negative bacilli; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases.

K. pneumoniae had a higher propensity to develop a BSI caused by the same colonizing pathogen compared with patients colonized by ST512 KPC-producing *K. pneumoniae* [19]. Moreover, MBL are able to inactivate all β-lactams including the β-lactam β-lactamase inhibitors ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam. Colistin often remains the unique active antibiotic, although several observational studies have demonstrated that treatment with colistin in patients with BSI by MBL CRE is associated with higher mortality and increased nephrotoxicity compared with the combination of ceftazidime-avibactam plus aztreonam [5]. In the ALARICO study, ceftazidime-avibactam was available for clinical use, and the majority of BSIs due to KPC-CRE were treated with this drug combination (155 of 304, 50.7%), while in the group of MBL-producing BSIs, colistin remained the most commonly used drug alone or in combination (48 of 77, 62.3%). Thus, we cannot exclude that the increased risk of mortality observed in MBL-producing infections is in part related to the regimens used for targeted therapy (most recent guidelines indicate the ceftazidime-avibactam plus aztreonam combination as the first-choice regimen [35-37]). The impact of new authorized antibiotics compared with colistin should be investigated in future randomized clinical trials.



Number at risk

CS-GNB	723	695	677	669	654	637	624
KPC	304	278	263	255	246	243	223
MBL	77	65	62	53	52	51	49
CRPA	61	61	56	54	49	45	41
CRAB	111	98	89	84	75	70	63

Figure 4. Survival curves (inverse probability weighting) according to the study groups. Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CS, carbapenem-susceptible; GNB, gram-negative bacilli; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase.

Early appropriate antibiotic therapy was associated with decreased risk of mortality in our cohort. Time from BSI onset to adequate antibiotic therapy has been associated with improved outcome in patients with KPC-producing CRE BSI [6]. It should be emphasized that we evaluated the impact of early appropriate therapy but we did not explore the role of specific antibiotic regimens on patient outcomes. Thus, future studies are warranted to explore the outcome of patients who receive different in vitro active empiric antibiotics.

Our study was conducted in Italy, a country with a high incidence of CR GNB. Local epidemiology and, even more important, local diagnostics may have influenced the estimation of attributable mortality in our study. Thus, data may have low generalizability in countries with low prevalence of resistant GNB, but the Italian experience may be pivotal for other countries to understand the impact of MDR organisms in clinical practice.

Second, estimation of AMR-attributable mortality is challenging, and we recognize the pitfalls of interpreting and calculating these data. In this study, we calculated the attributable mortality using a previously developed formula [23]. Although it is based on aORs, the causality between AMR and mortality is difficult to demonstrate with certainty and may not reflect the proportion of deaths for which exposure (CR GNB infection) was the etiological cause of death. As a matter of fact, in clinical practice, these patients are usually severely ill and at high risk of mortality due to hospital complications. Unfortunately, there is no mathematical formula that completely eliminates all of these potential confounding factors [38], and some factors, such as disease severity and frailty, may not be assessed by this observational study [39]. To mitigate our results, we interpreted the attributable mortality as an association instead of direct causation between CR GNB and death.

Moreover, some BSI cases may not have been included because of limited staff resources at some centers. Finally, we did not explore the role of specific antibiotic regimens on mortality; however, our findings may reflect an accurate image of real-life management of difficult-to-treat GNB infections.

CONCLUSIONS

In conclusion, CR GNB represent a threat for patients with BSI and are associated with a high risk of mortality. MBL-producing Enterobacterales represent the pathogens with the highest attributable mortality, followed by CRPA and CRAB. Prevention and surveillance strategies should be implemented in the hospital setting to avoid unfavorable outcomes attributable to CR GNB infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted

materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. M. F. designed the study. M. F. and G. T. analyzed the data and wrote the initial manuscript draft. A. F. performed the center-specific fixed-effects logistic analysis. M. F., M. V., and F. M. critically revised the manuscript for important intellectual content. S. C., A. M., G. D. C., A. C., A. M., M. F. M., A. E. M., R. S., L. D., L. C., M. M., A. A. M., M. L. E., C. G., C. S., R. F. D. V., G. C., A. A., C. B., S. T., G. R., G. F., G. D. S., A. F., C. I., S. C., U. M., F. P., I. G., T. S., A. C., N. C., and B. C. were responsible for data collection and revised the final manuscript. All authors contributed to data interpretation and to the review and editing of the manuscript. M. F. and G. T. accessed and verified the data. All authors had final responsibility for the decision to submit for publication.

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