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MAJOR ARTICLE

Clinical Outcomes and Bacterial Characteristics of Carbapenem-resistant *Acinetobacter baumannii* Among Patients From Different Global Regions

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Background. Carbapenem-resistant *Acinetobacter baumannii* (CRAb) is 1 of the most problematic antimicrobial-resistant bacteria. We sought to elucidate the international epidemiology and clinical impact of CRAb.

Methods. In a prospective observational cohort study, 842 hospitalized patients with a clinical CRAb culture were enrolled at 46 hospitals in five global regions between 2017 and 2019. The primary outcome was all-cause mortality at 30 days from the index culture. The strains underwent whole-genome analysis.

Results. Of 842 cases, 536 (64%) represented infection. By 30 days, 128 (24%) of the infected patients died, ranging from 1 (6%) of 18 in Australia-Singapore to 54 (25%) of 216 in the United States and 24 (49%) of 49 in South-Central America, whereas 42 (14%) of non-infected patients died. Bacteremia was associated with a higher risk of death compared with other types of infection (40 [42%] of 96 vs 88 [20%] of 440). In a multivariable logistic regression analysis, bloodstream infection and higher age-adjusted Charlson comorbidity index were independently associated with 30-day mortality. Clonal group 2 (CG2) strains predominated except in South-Central America, ranging from 216 (59%) of 369 in the United States to 282 (97%) of 291 in China.

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Acquired carbapenemase genes were carried by 769 (91%) of the 842 isolates. CG2 strains were significantly associated with higher levels of meropenem resistance, yet non-CG2 cases were over-represented among the deaths compared with CG2 cases.

Conclusions. CRAb infection types and clinical outcomes differed significantly across regions. Although CG2 strains remained predominant, non-CG2 strains were associated with higher mortality.

Clinical Trials Registration. NCT03646227.

Keywords. carbapenem-resistant *Acinetobacter baumannii*; clinical impact; international epidemiology.

Carbapenem-resistant *Acinetobacter baumannii* (CRAb) has emerged as a significant healthcare-associated pathogen over the last 2 decades [1]. Mortality rates associated with CRAb infections are high [2]; however, CRAb is often detected in patients with poor baseline health status or significant underlying conditions, and its true impact on their disease courses remains undefined. The ascendancy of CRAb in healthcare facilities during the past 2 decades coincides with the propagation of several dominant clonal lineages, especially clonal group 2 (CG2) [3, 4]. CG2 strains producing acquired OXA-23 carbapenemases appear to account for a large proportion of CRAb worldwide, yet regional differences have also been recognized [5]. How these strain differences define clinical features and patient outcomes remains unclear.

In this analysis, we explored the clinical features of patients with CRAb and the impact of infection over colonization in an international prospective cohort. Furthermore, we delineated the phenotypic and genomic characteristics of the CRAb isolates to highlight similarities and differences across regions.

METHODS

Study Design and Patients

The Study Network of *Acinetobacter baumannii* as Carbapenem-Resistant Pathogen (SNAP) is an international, prospective, observational, multicenter study with consecutive enrollment of hospitalized patients from whom CRAb was isolated during their hospitalization. Surveillance cultures were excluded. The first qualifying culture episode during the initial admission was included for each patient enrolled during the study period, which occurred between September 2017 and November 2019, depending on regions. Patients were enrolled from 46 health systems in 10 countries. The study was approved by the Institutional Review Boards of all the participating health systems with a waiver of consent. This study is registered with ClinicalTrials.gov (Clinical Trials Registration NCT03646227).

Carbapenem resistance was defined by a minimum inhibitory concentration (MIC) value of 8 mg/L or greater for meropenem, imipenem, or doripenem [6]. A patient was eligible without age exclusion if *A. baumannii* was identified from a clinically indicated culture specimen and was resistant to at least 1 of the 3 carbapenems tested at the local microbiology laboratory. Meropenem resistance was confirmed by MIC testing at central research laboratories, and cases with meropenem-resistant isolates were included in the final analysis.

Clinical Data Collection

Demographic and clinical data were obtained from electronic health records (EHRs). Infections were defined by published criteria [7], with the exception of respiratory cultures for which the clinical diagnosis recorded by the treating clinicians was applied based on review of the EHR [8]. Association with healthcare was determined as previously defined [9]. Positive cultures that did not meet the criteria for infection were considered to represent non-infection. At 90 days after discharge, data on post-hospitalization death and readmission were collected from the EHR.

Outcomes

Patient outcomes were evaluated at 30 and 90 days from the collection date of the index culture. For patients with infection, the primary outcome was all-cause mortality at 30 days. Secondary outcomes included the desirability of outcome ranking (DOOR) and 90-day all-cause mortality [10]. DOOR is an ordinal outcome that globally assesses patient wellbeing. The categories were: clinical response at 30 days with no events, 1 event, 2 or 3 events, and death, where the possible events included lack of clinical response at 30 days, worsening clinical status at discharge within 30 days or readmission within 30 days, and renal failure post-culture or *Clostridioides difficile* infection [7].

Microbiologic and Sequencing Analysis

The CRAb isolates were sent to central research laboratories, where the MICs of meropenem and other agents with anti-*Acinetobacter* activity were determined using the broth microdilution method.

Sequencing of the genomic DNA extracted from the first isolates of the enrolled patients was conducted using Illumina sequencers [11]. Draft genomes were assembled using SPAdes, version 3.13.1 [12]. *Acinetobacter* species were determined by fastANI, version 1.32, using a 95% cutoff for species identification [13, 14]. Multilocus sequence typing (MLST) was analyzed by MLST, version 2.22.0, using the PubMLST database [15, 16]. Clonal groups were defined as a central ST with its single-locus variants (SLVs) and their SLVs [17]. Resistance genes were identified by AMRFinderPlus, version 3.10.21, and ARIBA,

version 2.14.6 [18, 19]. Acquired carbapenemase genes were those other than $bla_{\text{OXA-51-like}}$ intrinsic to the species. Capsular polysaccharide locus and lipooligosaccharide outer core locus were defined using Kaptive version 2.0.3 [20]. Core genome alignment was generated by Snippy, version 4.6.0, using the *A. baumannii* AYE genome (accession no. NC_010410) as the reference [11]. A maximum likelihood phylogenetic tree was constructed in RAxML, version 8.2.4 [21].

Statistical Analysis

The characteristics of patients with CRAb and their outcomes were compared. The distributions of continuous variables, including ordered categorical variables, were compared using the Kruskal-Wallis test. The Pearson χ^2 test across groups was used for nominal categorical variables. To compare outcomes between infected and non-infected patients, both unadjusted and inverse probability weighting-adjusted pairwise DOOR analyses were performed, adjusting for region, immunocompromising conditions, pre-admission location, and age-adjusted Charlson comorbidity index (CCI) [22]. Pairwise DOOR comparisons estimated the probability of a more favorable outcome for a randomly selected patient with CRAb infection versus CRAb non-infection. Pairwise DOOR comparisons between geographic regions were also estimated. Among the infected patients, risk factors for outcomes were sought in exploratory logistic regression analyses that included anatomical source of infection, age-adjusted CCI of the patients, immunocompromising conditions, pre-admission location, monomicrobial infection, geographic region, clonal group, acquired carbapenemase gene (presence or absence), capsular polysaccharide locus and lipooligosaccharide outer core locus of the associated strains as variables of clinical and bacteriological interest, with study site as a random effect. *P* values <.05 were considered statistically significant, and all tests were 2-sided. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

Patient Characteristics

A total of 990 patients were enrolled at international sites participating in the Multi-Drug Resistant Organism (MDRO) Network (NCT03646227). After excluding 148 patients for various reasons, 842 patients were included in the primary analysis (Supplementary Table 1). The final cohort included 369 (44%) patients from the United States, 291 (35%) patients from China, 77 (9%) patients from the Middle East, 74 (9%) patients from South-Central America, and 31 (4%) patients from Australia-Singapore (Table 1). Males accounted for 55%–87% of the cohort depending on the region. Patients in South-Central America were significantly younger (median age 56; interquartile range [IQR] 38–68) than patients in the United States (median age 62; IQR 53–72), China (median age 63; IQR 48–73), Middle East (median age 63; IQR 32–74), or Australia-Singapore (median age 65; IQR 53–72; $P = .06$ across regions). Patients in South-Central America (median CCI 1; IQR 0–2) and China (median CCI 1; IQR 0–3) had fewer comorbidities than patients in the United States (median CCI 3; IQR 1–5), Middle East (median CCI 2; IQR 0–3), or Australia-Singapore (median CCI 2; IQR 0–3; $P < .0001$ across regions).

Overall, 536 (64%) of the 842 patients had CRAb infections, and 306 (36%) had CRAb non-infection. Additionally, 328 (70%) of the 468 respiratory tract isolates, 75 (44%) of the 170 wound isolates, and 19 (41%) of the 46 urinary isolates represented infection. In terms of acquisition, 523 (62%) of the 842 CRAb cases were defined as hospital-acquired and another 259 (31%) as healthcare-associated but non-hospital–acquired. Overall, 430 (51%) of the 842 patients with a CRAb infection were in an intensive care unit at the time of the first CRAb culture, ranging from 7 (23%) of 31 in Australia-Singapore to 175 (60%) of 291 in China, and 45 (61%) of 74 in South-Central America.

The most common sources of CRAb were the respiratory tract (n = 468, 56% of total), followed by wound (n = 170, 20%), bloodstream (n = 96, 11%), and urine (n = 46, 5%) (Table 1). The respiratory tract was particularly a common source in China (228 [78%] of 291 isolates), whereas South-Central America had a relatively high proportion of bloodstream isolates (20 [27%] of 74) compared with other regions, ranging from 1 (3%) of 31 in Australia-Singapore to 11 (14%) of 77 in the Middle East. An additional organism other than CRAb grew in 340 (40%) of the 842 patients from the same source. Concomitant growth was particularly common in wounds (48 of 75 infection cases and 61 of 95 non-infection cases, both 64%), for which methicillin-resistant *Staphylococcus aureus* (22 of 109 polymicrobial wound isolates) and *Pseudomonas* spp. (22 of 109) accounted for 20% each.

Strain Characteristics

An acquired carbapenemase gene was detected in 769 (91%) of 842 isolates. The proportion of CRAb isolates with an acquired carbapenemase was high across the regions, ranging from 305 (83%) of 369 isolates in the United States to 100% in the Middle East (n = 77) and Australia-Singapore (n = 31) (Figure 1). Also, $bla_{\text{OXA-23}}$ was the most common acquired carbapenemase gene across all regions and was present in 680 isolates (88%), including 9 with another acquired carbapenemase gene. And $bla_{\text{OXA-24/40}}$ was the next most commonly acquired carbapenemase gene and was present in 75 isolates (10%), including 3 isolates co-harboring $bla_{\text{OXA-23}}$. The other acquired carbapenemase genes were $bla_{\text{NDM-1}}$ (n = 11), $bla_{\text{OXA-58}}$ (n = 8), and $bla_{\text{OXA-237}}$, a $bla_{\text{OXA-134}}$-like carbapenemase gene only found in the United States (n = 5).

Table 1. Characteristics of Patients With CRAb Isolates by Region

Characteristics	United States (n = 369)	China (n = 291)	South-Central America (n = 74)	Middle East (n = 77)	Australia-Singapore (n = 31)	Total (n = 842)	*P* Value[a]
Demographics							
Age, y	62 (53–72)	63 (48–73)	56 (38–68)	63 (32–74)	65 (53–72)	62 (49–73)	.055
Female sex	167 (45)	86 (30)	33 (45)	20 (26)	4 (13)	310 (37)	<.0001
Comorbidities							
Charlson comorbidity index	3 (1–5)	1 (0–3)	1 (0–2)	2 (0–3)	2 (0–3)	2 (1–4)	<.0001
Diabetes	178 (48)	74 (25)	19 (26)	35 (45)	14 (45)	320 (38)	<.0001
Heart disease	131 (36)	46 (16)	6 (8)	27 (35)	6 (19)	216 (26)	<.0001
Cerebrovascular disease	87 (24)	63 (22)	3 (4)	13 (17)	3 (10)	169 (20)	.0014
Chronic kidney disease	53 (14)	17 (6)	5 (7)	17 (22)	3 (10)	95 (11)	.0001
COPD	97 (26)	21 (7)	10 (14)	5 (6)	5 (16)	138 (16)	<.0001
History of malignancy	54 (15)	36 (12)	4 (5)	6 (8)	5 (16)	105 (12)	.14
Immunocompromised	26 (7)	13 (4)	7 (9)	3 (4)	1 (3)	50 (6)	.34
Origin of patient	…	…	…	…	…	…	<.0001
Home	112 (30)	109 (37)	61 (82)	51 (66)	18 (58)	351 (42)	…
Long-term care facility	155 (42)	4 (1)	0 (0)	0 (0)	1 (3)	160 (19)	…
Long-term acute care	47 (13)	17 (6)	0 (0)	0 (0)	1 (3)	65 (8)	…
Hospital transfer	51 (14)	161 (55)	10 (14)	24 (31)	3 (10)	249 (30)	…
International transfer	4 (1)	0 (0)	3 (4)	2 (3)	8 (26)	17 (2)	…
Prior ICU admission	203 (55)	204 (70)	55 (74)	56 (73)	11 (35)	529 (63)	<.0001
Patient location at time of first positive culture	…	…	…	…	…	…	<.0001
Emergency department	42 (11)	8 (3)	5 (7)	1 (1)	1 (3)	57 (7)	…
ICU	163 (44)	175 (60)	45 (61)	40 (52)	7 (23)	430 (51)	…
Medical ward	125 (34)	59 (20)	14 (19)	23 (30)	14 (45)	235 (28)	…
Surgical ward	17 (5)	42 (14)	5 (7)	9 (12)	8 (26)	81 (10)	…
Hematology/oncology ward	4 (1)	1 (0)	0 (0)	1 (1)	0 (0)	6 (1)	…
Other	18 (5)	6 (2)	5 (7)	3 (4)	1 (3)	33 (4)	…
Days from admission to culture	2 (1–7)	7 (2–15)	16 (9–31)	17 (1–42)	12 (3–26)	5 (1–15)	<.0001
Hospital-acquired/ healthcare-associated	…	…	…	…	…	…	<.0001
Hospital-acquired	166 (45)	216 (74)	64 (86)	53 (69)	24 (77)	523 (62)	…
Healthcare-associated, non-hospital-acquired	163 (44)	67 (23)	6 (8)	17 (22)	6 (19)	259 (31)	…
Non-healthcare/ non-hospital-acquired	40 (11)	8 (3)	4 (5)	7 (9)	1 (3)	60 (7)	…
Infection/non-infection by source	…	…	…	…	…	…	<.0001
Blood (infection only)	41 (11)	23 (8)	20 (27)	11 (14)	1 (3)	96 (11)	…
Respiratory (all)	163 (44)	228 (78)	25 (34)	41 (53)	11 (35)	468 (56)	…
Infection	103 (28)	180 (62)	20 (27)	18 (23)	7 (23)	328 (39)	…
Colonization	60 (16)	48 (16)	5 (7)	23 (30)	4 (13)	140 (17)	…
Urine (all)	18 (5)	7 (2)	7 (9)	6 (8)	8 (26)	46 (5)	…
Infection	6 (2)	2 (1)	4 (5)	1 (1)	6 (19)	19 (2)	…
Colonization	12 (3)	5 (2)	3 (4)	5 (6)	2 (6)	27 (3)	…
Wound (all)	135 (37)	8 (3)	10 (14)	8 (10)	9 (29)	170 (20)	…
Infection	60 (16)	4 (1)	3 (4)	4 (5)	4 (13)	75 (9)	…
Colonization	75 (20)	4 (1)	7 (9)	4 (5)	5 (16)	95 (11)	…
Other (all)	12 (3)	25 (9)	12 (16)	11 (14)	2 (6)	62 (7)	…
Infection	6 (2)	10 (3)	2 (3)	0 (0)	0 (0)	18 (2)	…
Colonization	6 (2)	15 (5)	10 (14)	11 (14)	2 (6)	44 (5)	…
Pitt bacteremia score	4 (2–6)	4 (1–6)	4 (1–6)	4 (2–6)	2 (0–5)	4 (2–6)	.13
Polymicrobial[b]	202 (55)	79 (27)	21 (28)	24 (31)	14 (45)	340 (40)	<.0001

All data are shown as n (% of total) or median (interquartile range).

Abbreviations: COPD, chronic obstructive pulmonary disease; CRAb, carbapenem-resistant *Acinetobacter baumannii*; ICU, intensive care unit.

[a] *P*- values to assess differences among groups. The χ^2 test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables.

[b] Monomicrobial and unknown were combined; n (%) for polymicrobial are shown.

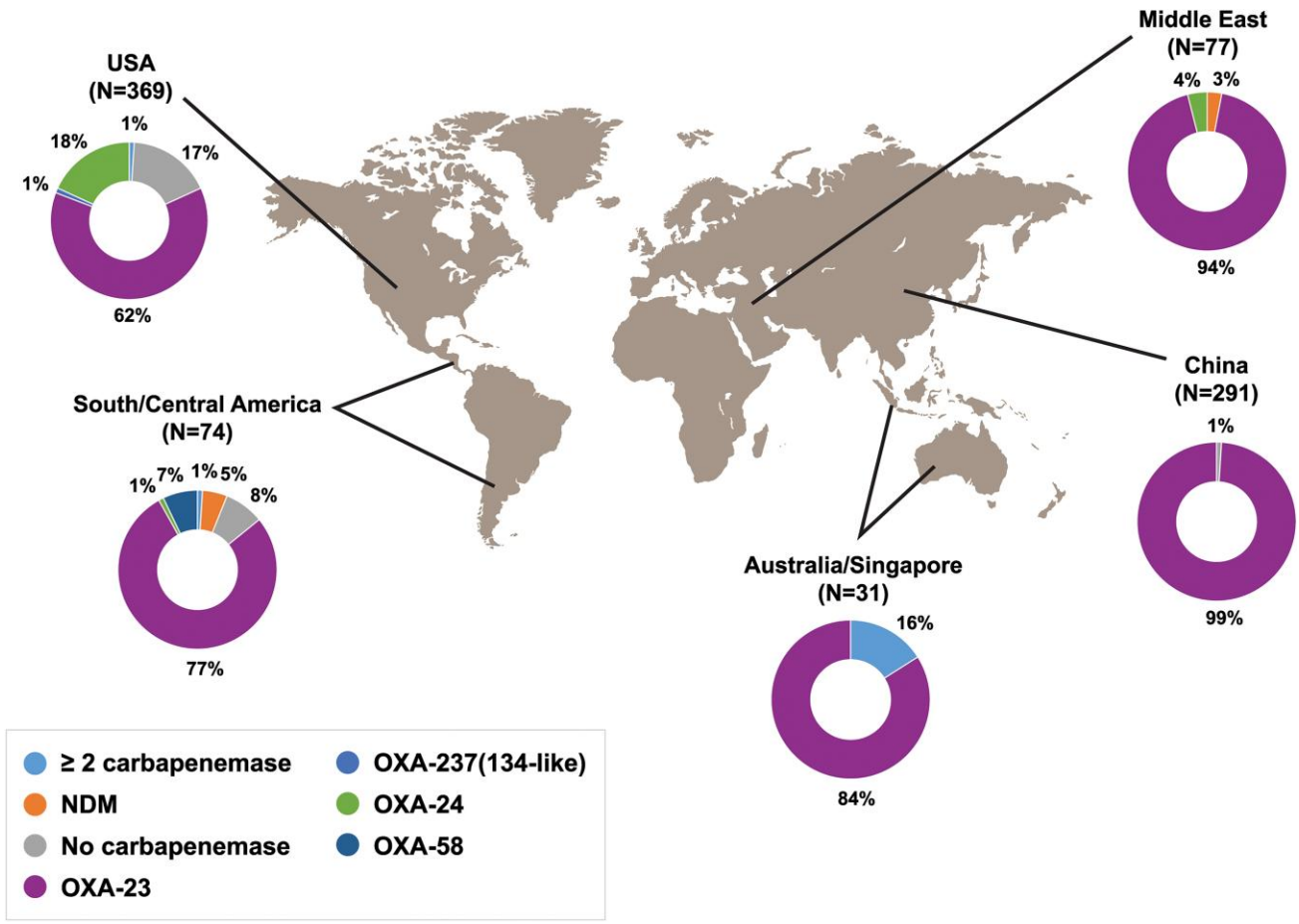

Figure 1. Acquired carbapenemases among CRAb isolates by region. CRAb isolates carried genes for the following acquired carbapenemases: USA: OXA-23 (n = 228), OXA-24 (n = 68), OXA-237 (n = 4), OXA-23 + OXA-24 (n = 3), OXA-23 + OXA-237 (n = 1), and OXA-58 (n = 1); China: OXA-23 (n = 288); South-Central America: OXA-23 (n = 57), OXA-58 (n = 5), NDM (n = 4), OXA-58 + NDM (n = 1), and OXA-24 (n = 1), ; Middle East: OXA-23 (n = 72), OXA-24 (n = 3), and NDM (n = 2); and Australia-Singapore: OXA-23 (n = 26), OXA-23 + NDM (n = 4), and OXA-23 + OXA-58 (n = 1). Abbreviation: CRAb, carbapenem-resistant *Acinetobacter baumannii*.

Carbapenemase-producing isolates were more likely to have meropenem MICs ≥32 mg/L than non-carbapenemase–producing isolates (Supplementary Figure 1). Of 769 CRAb isolates with an acquired carbapenemase gene, 749 (97%) had meropenem MICs of ≥32 mg/L compared with 55 (75%) of 73 isolates without an acquired carbapenemase gene ($P < .0001$). Resistance rates to non-carbapenem agents were variable, but overall were high, except for polymyxins (Supplementary Table 2).

Molecular Epidemiology

CG2 accounted for 598 of 842 CRAb isolates (71%) and was the most common clonal group in all regions with the exception of South-Central America, where only 3 (4%) isolates belonged to CG2 (Figure 2). In South-Central America, the isolates were much more diverse, with CG1 and CG25 being the most common (both 21 [28%] of 74), followed by CG15 and CG79 (both 11 [15%] of 74). In the United States (n = 369), the most common clonal groups after CG2 (n = 216) were CG499 (n = 77) and CG406 (n = 31), accounting for 21% and 8% and identified from 10 and 6 health systems, respectively.

CG2 was associated with higher meropenem MICs; meropenem MIC was >32 mg/L in 383 (64%) of the 598 CG2 isolates and 134 (55%) of the 244 non-CG2 isolates (Wilcoxon rank sum $P = .023$). CG2 was also associated with multidrug resistance toward other agents (Supplementary Table 3). CG2 was also significantly associated with the presence of $bla_{\text{OXA-23}}$ as the acquired carbapenemase gene compared with non-CG2 (516 [96%] of 598 vs 155 [66%] of 244; $P < .0001$) (Supplementary Table 4).

Clinical Outcomes

In the overall cohort of 842 patients, 170 patients (20%; 95% confidence interval [CI] 17–23) died within 30 days. Of the 536 patients who had a CRAb infection, 128 patients (24%; 95% CI 20–27) died within 30 days compared with 42

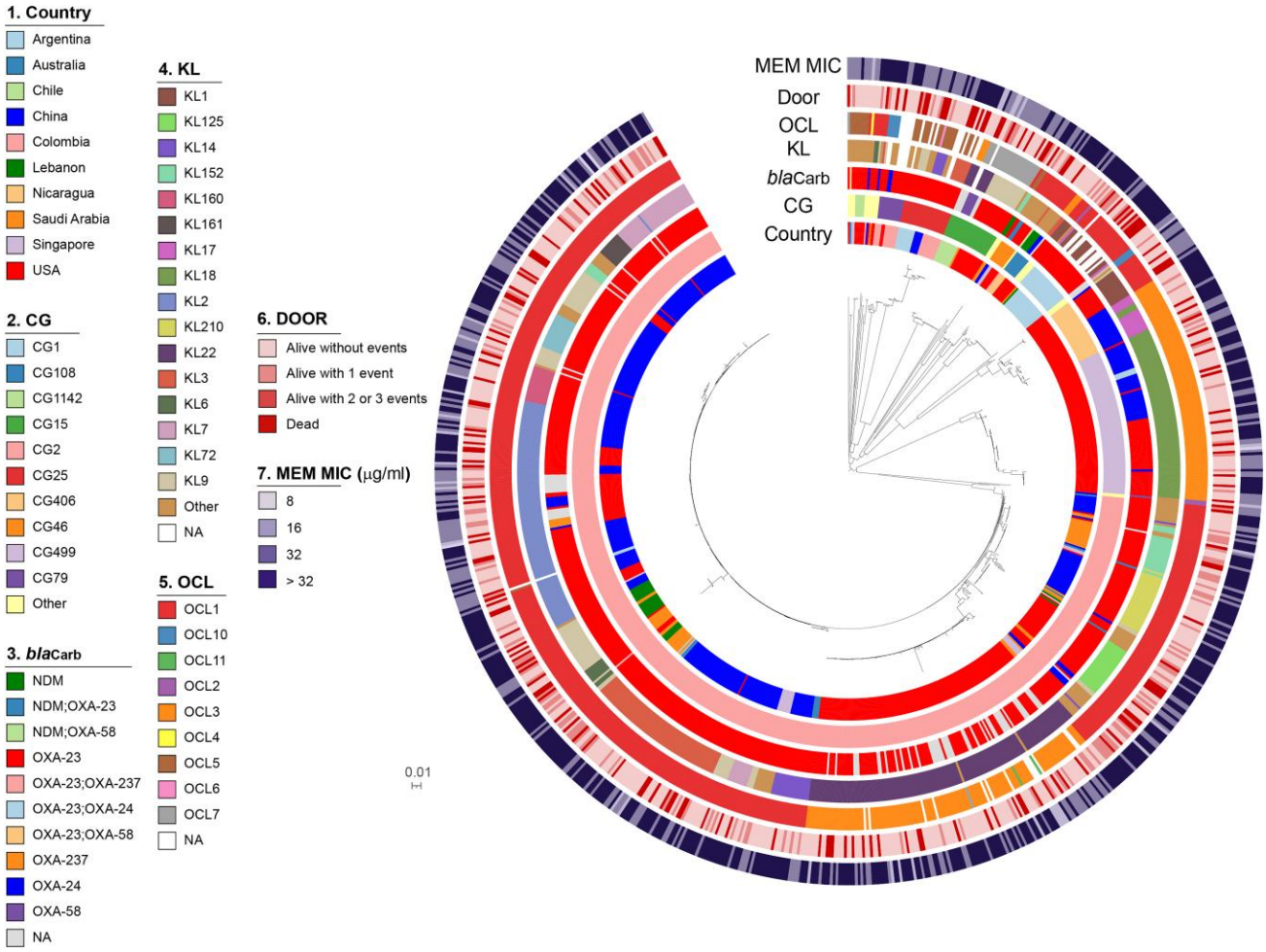

Figure 2. Population structure of CRAb isolates based on WGS. Phylogenetics are linked with country, clonal group (CG), acquired carbapenemase, capsular polysaccharide locus (KL), lipooligosaccharide outer core locus (OCL), DOOR outcome, and meropenem (MEM) MIC value. Abbreviations: CRAb, carbapenem-resistant *Acinetobacter baumannii*; DOOR, desirability of outcome ranking; MIC, minimum inhibitory concentration; NA, not applicable; WGS, whole-genome sequencing.

(14%; 95% CI 10–18) of 306 non-infected patients (difference: 10%, 95% CI 5–15). The unadjusted and inverse probability-weighted DOOR values for non-infected patients over infected patients were 58% (95% CI 54–61) and 59% (95% CI 55–62), respectively, meaning that a randomly selected non-infected patient had a 58% probability of a more favorable outcome than a randomly selected infected patient, with the 95% CI ruling out 50%. By infection types, 30-day mortality rates were 42% (40 of 96, 95% CI 32–52) for bloodstream infections, 23% (75 of 328, 95% CI 18–27) for respiratory infections, 11% (8 of 75, 95% CI 4–18) for wound infections, and 11% (2 of 19, 95% CI 0–24) for urinary tract infections ($P < .0001$) (Supplementary Figure 2). Monomicrobial infection was associated with higher mortality rates than polymicrobial infection at both 30 days (89 [28%] of 320 vs 38 [18%] of 211; difference: 10%, 95% CI 2–17) and 90 days (105 [33%] of 320 vs 50 [24%] of 211; difference: 9%, 95% CI 1–17) (Supplementary Table 5). This was driven by high mortality rates of monomicrobial bloodstream infection (Supplementary Table 6).

Overall, the 30-day mortality rates for infected patients were uneven across the regions: 49% (24 of 49, 95% CI 35–63) in South-Central America, 25% (54 of 216, 95% CI 19–31) in the United States, 20% (43 of 219, 95% CI 14–25) in China, 18% (6 of 34, 95% CI 5–30) in the Middle East, and 6% (95% CI 0–16) in Australia-Singapore ($P = .0001$). In the DOOR outcomes, the proportion with the most desirable outcome (ie alive without events) was highest in China (79 [36%] of 219; 95% CI 30–42), followed by the United States (74 [34%] of 216; 95% CI 28–41), the Middle East (7 [21%] of 34; 95% CI 7–34), South-Central America (9 [18%] of 49; 95% CI 8–29), and Australia-Singapore (2 [11%] of 18; 95% CI 0–26) (Table 2; Supplementary Figures 3-5).

The presence of an acquired carbapenemase gene was not associated with mortality at either 30 or 90 days (Supplementary Tables 7, 8). Patients with non-CG2 isolates were significantly

Table 2. Clinical Outcomes of Patients Infected With CRAb by Region

Characteristics	United States (n = 216)	China (n = 219)	South-Central America (n = 49)	Middle East (n = 34)	Australia-Singapore (n = 18)	Total (n = 536)	*P* Value[a]
Mortality[b]							
30-day (primary outcome)	54 (25)	43 (20)	24 (49)	6 (18)	1 (6)	128 (24)	.0001
Risk difference (vs United States, 95% CI)	…	−5 (−13 to 2)	24 (9–39)	−7 (−19 to 9)	−20 (−28 to 1)	…	…
90-day	65 (30)	49 (22)	26 (53)	10 (29)	6 (33)	156 (29)	.0009
Risk difference (vs United States, 95% CI)	…	−8 (−16 to 1)	23 (8–38)	−1 (−15 to 17)	3 (−15 to 27)	…	…
Length of hospital stay from index culture	9 (4–18)	15 (7–24)	15 (7–28)	34 (6–62)	33 (14–43)	12 (5–24)	<.0001
DOOR outcome at 30 d[c] (Supplementary Figure 3)							
Alive without events	74 (34)	79 (36)	9 (18)	7 (21)	2 (11)	171 (32)	…
Alive with 1 event	60 (28)	63 (28)	6 (12)	7 (21)	6 (33)	142 (26)	…
Alive with 2 or 3 events	28 (13)	35 (16)	10 (20)	14 (41)	9 (50)	96 (18)	…
Death	54 (25)	43 (20)	24 (49)	6 (18)	1 (6)	128 (24)	…
DOOR probability % (vs United States, 95% CI)	…	52 (47–57)	34 (26–43)	43 (34–52)	43 (34–53)	…	…
Disposition after discharge	…	…	…	…	…	…	<.0001
Home	31 (14)	72 (33)	17 (35)	21 (62)	9 (50)	150 (28)	…
Long-term care facility	64 (30)	3 (1)	0 (0)	0 (0)	2 (11)	69 (13)	…
Long-term acute care	46 (21)	2 (1)	1 (2)	0 (0)	1 (6)	50 (9)	…
Transfer to another hospital	8 (4)	72 (33)	3 (6)	1 (3)	1 (6)	85 (16)	…
Hospice	22 (10)	21 (10)	3 (6)	0 (0)	0 (0)	46 (9)	…
Death	44 (20)	49 (22)	25 (51)	11 (32)	4 (22)	133 (25)	…
Transfer to a foreign country	1 (0)	0 (0)	0 (0)	1 (3)	1 (6)	3 (1)	…
Clinical response	107 (50)	86 (39)	12 (24)	13 (38)	6 (33)	224 (42)	.013

All data are shown as n (% of total) or median (interquartile range).

Abbreviations: CI, confidence interval; CRAb, carbapenem-resistant *Acinetobacter baumannii*; DOOR, desirability of outcome ranking.

[a] *P*- values to assess differences among groups. The χ^2 test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables.

[b] Patients who were discharged to hospice were not considered to have died. When discharge to hospice was combined with death, the DOOR outcomes at 30 d were: alive without events, 73 (34%); alive with 1 event, 53 (25%); alive with 2 or 3 events, 27 (13%); deceased, 63 (29%) for the United States, and alive without events, 77 (35%); alive with 1 event, 45 (21%); alive with 2 or 3 events, 35 (16%); deceased, 62 (28%) for China; and no changes for the other regions.

[c] The three adverse events assessed by DOOR were: lack of clinical response, lack of discharge within 30 d or readmission within 30 d, and incident renal failure or *Clostridioides difficile* infection.

more likely to die by 30 days than those with CG2 isolates (48 [33%] of 147 vs 80 [21%] of 389; difference: 12%; 95% CI 4–21) (Supplementary Tables 9, 10). The excess mortality of non-CG2 cases over CG2 cases was also observed at 90 days (58 [39%] of 147 vs 98 [25%] of 389; difference: 14%; 95% CI 5–23).

Risk Factors for Mortality

An exploratory analysis was conducted to probe for risk factors associated with 30-day mortality among patients with infection. In the univariable fixed-effect model, region (South-Central America compared with the United States), anatomical source of infection (blood compared with respiratory, wound, urine), clonal group (CG1, CG15, CG25 compared with CG2), age-adjusted CCI, monomicrobial infection, and lipooligosaccharide outer core locus (OCL; OCL1, OCL3 compared with others) were significant risk factors for 30-day mortality. In the multivariable model, bloodstream infection (compared with wound and urinary tract infection), monomicrobial infection, and higher age-adjusted CCI were significant risk factors for 30-day mortality among infected patients (Supplementary Table 11).

DISCUSSION

In this analysis, large variations were observed in the sources of CRAb and the types of infection depending on region. Almost 80% of CRAb isolates were identified from respiratory specimens in China compared with 34%–53% from other regions. Similar observations were made with the Prospective Observational *Pseudomonas* (POP) study, a sister MDRO Network study on carbapenem-resistant *Pseudomonas aeruginosa* [8]. On the other hand, blood and wounds were common sources of CRAb in South-Central America and the United States relative to other regions, respectively. These differences may be associated with infecting bacteria, host susceptibility, or differences in healthcare delivery, and indicate that CRAb poses distinct sets of clinical challenges depending on the regions.

The global spread of CRAb has been driven by several major lineages, including clonal groups CG1, CG2, and CG79, with CG2 by far the most predominant [3]. The predominance of CG2 was corroborated in our study in all regions except in South-Central America, where non-CG2 lineages accounted for the majority of strains, supporting the unique CRAb molecular epidemiology across South-Central America [23].

In the United States, CG499 was among the isolates in 10 hospital systems confirming broad dissemination of this clonal group, which was previously reported in the pilot portion of this cohort [24] and more recently in outpatient settings in Missouri [25]. CG406 was another clonal group only present among isolates from the United States, detected in 6 hospital systems at a lower frequency. CG406 isolates have been reported as early as 2005 in the United States [25]. Strain factors that favor their spread in the United States would be an important area of future investigation, as well as longitudinal surveillance to examine the trajectory of these emerging lineages.

Reported estimates of mortality associated with CRAb infection vary widely [26]. In our study, 24% of infected patients died within 30 days, which is likely representative of mortality associated with this condition today. In particular, the mortality rate of patients with bloodstream infection exceeded 40%. Striking geographic disparity in patient outcomes was also observed, with a particularly high mortality rate in South-Central America. This was despite patients in the region being younger and healthier at baseline. This observation may be associated with the higher incidence of bloodstream infection as well as unmeasured differences in patient characteristics, diagnostic and treatment approaches, or healthcare delivery. Furthermore, the excess mortality among South-Central American patients was not as prominent among those infected with carbapenem-resistant *P. aeruginosa* in the POP study or carbapenem-resistant *Enterobacterales* in CRACKLE-2, another MDRO Network study [8, 11]. This suggests that the characteristic of specific CRAb strains prevalent in the region may play a role in the excess mortality, including clonal group, carbapenemase production, and key immunogenic antigens, such as the capsular polysaccharide and lipooligosaccharide outer core [27]. When a model with 30-day mortality as the response variable was built, bloodstream infection, monomicrobial infection, and higher age-adjusted CCI were independent risk factors for death. On the other hand, none of the strain variables that were risk factors in the univariable analysis (clonal group, lipooligosaccharide outer core locus) and included in the multivariable model were independently associated with mortality. Further studies are needed to assess whether strain lineages unique to South-Central America are inherently more virulent than CG2.

Centralized susceptibility testing showed high rates of resistance across commonly used agents in addition to carbapenems. An exception was polymyxins (colistin and polymyxin B), which were active (now interpreted as intermediate for MICs $\leq$2 mg/L by the CLSI) against 88% of the strains, but their inherent characteristics, such as unpredictable pharmacokinetics and significant nephrotoxicity, challenge their routine use in the clinic [28]. Whether newer agents with robust anti-CRAb activity, such as cefiderocol [29] and sulbactam-durlobactam [30], will improve survival and other relevant clinical outcomes of patients remains to be seen.

Our study has several limitations. The cohort did not include hospitals from Europe and Africa, where the clinical and genome epidemiology of CRAb may differ. Additionally, the study was conducted through waiver of consent to sequentially enroll patients with the pathogen. The design restricted clinical data collection to documentations available in the EHR, but this also allowed us to describe an unbiased picture of CRAb and its clinical impact. In summary, CRAb infection types and patient outcomes differed significantly across the regions. CG2 was the predominant CRAb lineage in all regions except South-Central America, where non-CG2 lineages predominated. We also observed an increasing prevalence of non-CG2 lineages unique to the United States, which merits attention. The findings underscore the distinct clinical challenges posed by CRAb, as well as the need to recognize factors that may favor the emergence and spread of new lineages in certain regions.

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

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