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Influence of ACB complex genospecies on clinical outcomes in a U.S. hospital with high rates of multidrug resistance

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Summary

Objectives—Bacteria within the *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* (ACB) complex commonly cause nosocomial infection and are often multidrug resistant. Advances in genospecies typing allow for speciation within the ACB complex; however, little is known about the effect of genospecies on patient outcomes.

Methods—Adult patients with ACB complex bacteremia from Jan 2005–Oct 2012 were included. Bacterial isolates were speciated by *rpoB* gene sequence analysis, and clinical data were collected.

Results—Of 147 patients with ACB complex bacteremia, 116 had *A. baumannii* (78.9%), 28 had *A. pittii* (19.0%), and 3 had *A. nosocomialis* (2.0%). *A. baumannii* bacteremia was associated with greater comorbidity and was more frequently multidrug resistant (79% vs. 16%, $p < 0.01$). Multidrug resistant *A. baumannii* but not susceptible *A. baumannii* was associated with worse outcomes compared to non-*baumannii* ACB complex bacteremia. Neither multidrug resistance nor genospecies was an independent predictor of mortality, but receipt of appropriate therapy was associated with decreased risk of mortality (OR, 0.13; 95% CI, 0.04–0.44; $p < 0.01$).

Conclusions—*A. baumannii* bacteremia is associated with worse clinical outcomes than non-*baumannii* ACB complex bacteremia. The difference, however, appears to be related to multidrug resistance and attendant receipt of appropriate therapy rather than genospecies.

Keywords

Multidrug resistance; bacteremia; *Acinetobacter calcoaceticus*; *Acinetobacter baumannii*; genome

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Transparency declarations

The authors have none to declare.

Introduction

Acinetobacter baumannii is a common cause of nosocomial infections, particularly pneumonia and catheter-related bloodstream infections, and often causes clonal outbreaks in critically ill patients.^{1–3} Infections with *A. baumannii* have been associated with high attributable mortality and increased hospital length of stay.⁴ In addition, multidrug resistance is often a predictor of poor clinical outcomes in patients infected with *A. baumannii*.⁵ However, much of the difference in patient outcomes due to multidrug resistance may be explained by delays in the receipt of active antimicrobial therapy.^{6,7}

The *Acinetobacter* genus currently comprises 34 species, with the *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* (ACB) complex including four phenotypically related species: *A. baumannii*, *A. calcoaceticus*, *A. pittii* (formerly *Acinetobacter* genospecies 3), and *A. nosocomialis* (formerly *Acinetobacter* genospecies 13TU).^{8,9} Conventional microbiologic phenotypic identification cannot reliably distinguish these species and, as such, they are often reported clinically as “*Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex.” Advances in molecular genotyping and whole genome sequencing have made possible delineation of individual *Acinetobacter* species within clinical isolates of the ACB complex.

All species except *A. calcoaceticus* have been implicated in human disease. Infection with different ACB complex species may be associated with different risk factors and produce different clinical outcomes.^{10–16} In some studies, infection with *A. baumannii* has been associated with increased mortality^{10–13} while in others, the presence of multidrug resistance or inappropriate initial therapy is associated with increased mortality rather than genospecies.^{15,16} In addition, *A. baumannii* appears to be resistant to more classes of antimicrobial agents than other species in the ACB complex.¹⁷ Due to the potential differences in epidemiology, antimicrobial resistance, and clinical outcomes among members of the ACB complex, the current practice of reporting ACB complex infection without further speciation may be inadequate and lead to inferior clinical care.

Many of the existing studies on the impact of ACB complex genospecies on clinical outcomes were conducted at a small number of medical centers in Taiwan and gave heterogeneous results.^{10,11,13,15,16} Only one study has been conducted in the U.S., and it included a high proportion of carbapenem-susceptible isolates (93%), making it difficult to draw conclusions from this study about a predominantly MDR *A. baumannii* population.¹⁴ In addition, most of these studies used 16S rRNA internal transcribed spacer (ITS) gene sequencing for speciation.^{10,11,13,15,16} 16S rRNA sequencing may be insufficient for differentiating closely related bacterial species, especially when certain regions of the gene are included.^{18,19} Housekeeping gene sequence analysis can provide better resolution of species differences because these genes evolve faster than 16S rRNA genes.^{18,20} Although a number of genes have been investigated for *Acinetobacter* speciation, the *rpoB* gene is among the best described for this purpose.^{20–24}

In this study, we investigated the clinical characteristics, antimicrobial susceptibility patterns and outcomes associated with ACB complex bacteremia at a large, academic medical center

in the United States. To more accurately describe *Acinetobacter* genospecies variability in our population, we used the *rpoB* gene sequence for speciation.

Methods

Study population

This was a retrospective cohort study conducted at Northwestern Memorial Hospital (NMH), an approximately 900-bed tertiary-care academic medical center located in Chicago, IL. All adult patients (≥ 18 years old) with ACB complex cultured from 1 or more blood cultures between January 2005 – October 2012 were identified through the Clinical Microbiology Laboratory and were eligible for inclusion in the study. Patients whose blood cultures were felt to represent contamination and who were not treated for active infection were excluded. Only the first positive blood culture from patients with two or more positive blood cultures during a single hospital admission was included. This study was approved by the Institutional Review Board at Northwestern University with a waiver of informed consent.

Microbiologic studies

Phenotypic identification of blood cultures to the level of the ACB complex was performed in the Clinical Microbiology Laboratory using the Vitek2 system (bioMérieux, Marcy l'Etoile, France). Susceptibilities for most antibiotics also were performed using the Vitek2 system. Etests (bioMérieux) were used to determine colistin and tigecycline susceptibilities, and disk diffusion was used to determine piperacillin-tazobactam, minocycline and doxycycline susceptibilities. All susceptibilities were interpreted according to Clinical and Laboratory Standards Institute guidelines.²⁵ Minimum inhibitory concentrations (MICs) for tigecycline were interpreted according to the U.S. FDA breakpoints for Enterobacteriaceae, with MICs ≤ 2 µg/mL considered susceptible.²⁶ Frozen stocks of all bacterial isolates were maintained at –80°C.

Species identification

Isolates were streaked onto blood agar plates from the frozen stocks, and a single colony was inoculated into Luria-Bertani (LB) broth and grown overnight at 37°C. Genomic DNA was extracted from overnight cultures using either a Qiagen EZ1 Advanced robotic workstation (Valencia, CA) or a Promega Maxwell 16 instrument (Madison, WI) according to the manufacturer's instructions. Genomic DNA libraries were prepared and barcoded using the Nextera XT kit (Illumina, San Diego, CA). Equal amounts (200 ng) of each DNA library were pooled together and run on either an Illumina HiSeq 2000 system with 100-bp paired end reads or on an Illumina MiSeq system with 250-bp paired end reads. Sequencing was performed by the University of Maryland Institute for Genome Sciences, blinded to all clinical data. Raw sequence reads were then assembled *de novo* using Ray v2.3.0.²⁷ Low-quality assemblies, defined as a sequence size of assembled contigs ≤ 500 bp totaling more than 4.5 M bp, were excluded.

Further analysis of the whole genome sequencing data from our cohort will be reported separately, but for the purposes of this study the *rpoB* gene sequence was used to determine

the genospecies of the blood isolates.^{20,22} Zone 1 *rpoB* sequences were identified from the assembled whole genome sequences using an in-house *in silico* PCR script.²⁸ Briefly, assembly contigs were screened to identify sequence flanked by the primer sequences Ac696F (TAYCGYAAAGAYTTGAAAGAAG) and Ac1093R (CMACACCYTTGTTMCCRTGA) as described by La Scola et al.²⁴ *In silico* “amplified” sequences were identified by BLAST alignment against the NCBI nucleotide collection database.²⁹ Patients with bacteremia caused by mixed *Acinetobacter* genospecies were excluded.

Data collection

Data on demographics, underlying diseases, age-adjusted Charlson co-morbidity score,³⁰ laboratory testing, infection characteristics, treatment, and clinical outcomes were collected retrospectively from chart review. Sources of bacteremia were identified in accordance with Centers for Disease Control and Prevention/National Health Safety Network (CDC/NHSN) guidelines.^{30,31} If no source or multiple possible sources were identified, the bacteremia was labeled as primary.

Polymicrobial bacteremia was defined as growth of any other bacteria in the same culture from which ACB complex was grown. Immunosuppression was defined as underlying immunosuppressive disease, receipt of antineoplastic drugs or other immunosuppressive agents in the previous 4 weeks, or receipt of corticosteroids at an equivalent dose of 10 mg of prednisone for more than 3 days in the previous 2 weeks. Neutropenia was defined as an absolute neutrophil count < 500 cells/mm³. Hepatic dysfunction was defined as any liver function test value > 3 times the upper limit of normal at the time of culture. Renal dysfunction was defined as history of chronic kidney disease, current dialysis, or an increase in serum creatinine of 0.5 mg/dl or 50% at the time of culture. Multidrug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial categories.³² Healthcare-associated infection (HAI) was defined according to the CDC/NSHN surveillance definition.³⁰ Appropriate antibiotic treatment was defined as use of one or more antibiotics to which the isolate was susceptible. Time to appropriate therapy, time to negative cultures, hospital length of stay following positive culture, and both 14-day and 30-day mortality were also recorded.

Statistical analysis

For clinical and demographic characteristics, categorical variables were compared using the Fisher’s exact test and continuous variables were compared using the Mann-Whitney U test or Student’s t-test, as appropriate. The associations between clinical outcomes for patients with susceptible and MDR *A. baumannii* and susceptible and MDR non-*baumannii* ACB complex bacteremia were compared using the Kruskal–Wallis one-way analysis of variance (ANOVA) or Fisher’s exact test. Post-hoc tests using the Mann-Whitney U test or Fisher’s exact test and a Bonferroni-adjusted α level for pair-wise comparisons were performed if the results of the initial Kruskal–Wallis one-way ANOVA or Fisher’s exact test were significant. For the endpoint of 30-day mortality, variables that could plausibly be associated with the outcome and with a p-value of < 0.1 in the univariate analysis were considered for entry into a multivariate logistic regression model using a forward stepwise method. Time to mortality

was analyzed using the Kaplan-Meier survival analysis with the log-rank test. A p-value of < 0.05 was considered significant for all statistical tests. SPSS version 22.0 (Chicago, IL) was used for all statistical analyses.

Results

During the study period, 156 patients with 1 blood culture positive for the ACB complex were identified. Three patients with ACB complex bacteremia who were seen by an Infectious Diseases consultant and felt not to have active infection given a lack of SIRS criteria or other infectious symptoms at the time the culture was drawn were excluded. All three patients had prompt resolution of bacteremia without active antibiotic therapy. In addition, one patient whose culture contained mixed *Acinetobacter* genospecies and five patients whose cultures gave poor quality sequencing results despite multiple replicates and/or could not be speciated by *rpoB* analysis were excluded. Therefore, a total of 147 patients with ACB complex bacteremia were included: 116 *A. baumannii* (78.9%), 28 *A. pittii* (19.0%), and 3 *A. nosocomialis* (2.0%). Of note, there was one recognized outbreak of MDR *A. baumannii* during the study period, occurring between 2005–2006 and involving eight patients included in this study.

The clinical and demographic characteristics of patients with *A. baumannii* versus non-*baumannii* ACB complex bacteremia are listed in Table 1. Patients with non-*baumannii* ACB complex bacteremia were more likely to be female. Patients with *A. baumannii* bacteremia were more likely to have healthcare-associated infection, to require mechanical ventilation, to be in the ICU, to have a greater number of days of prior antibiotics, and to have diabetes and renal dysfunction. Most cases of bacteremia were associated with indwelling central catheters, although 11% of patients with *A. baumannii* bacteremia had a respiratory source. The proportions of *A. baumannii* and non-*baumannii* ACB complex identified among blood isolates were similar throughout the 7-year time period.

Table 2 lists the antimicrobial susceptibilities for *A. baumannii* and non-*baumannii* ACB complex isolates. When compared with non-*baumannii* ACB complex isolates, *A. baumannii* isolates exhibited decreased susceptibility to all antimicrobials tested except colistin, for which there was no significant difference in susceptibility (96% vs. 100%, $p = 1.0$). Only 24% of *A. baumannii* isolates were susceptible to tigecycline. Overall, *A. baumannii* isolates were also much more likely to be MDR (79% vs. 16%, $p < 0.01$).

To examine the impact of antimicrobial susceptibility in addition to genospecies, the clinical outcomes of patients with *A. baumannii* and non-*baumannii* ACB complex bacteremia were stratified by multidrug resistance (Table 3). There were no significant differences in outcomes between patients with susceptible *A. baumannii* and susceptible non-*baumannii* ACB complex or between patients with MDR *A. baumannii* and MDR non-*baumannii* ACB complex. However, MDR status was associated with higher 30-day and 14-day mortality in both the *A. baumannii* and non-*baumannii* ACB complex groups. In addition, patients with MDR *A. baumannii* were less likely to receive appropriate therapy than patients with susceptible *A. baumannii*. Of the 29 patients with MDR *A. baumannii* who did not receive appropriate therapy, 17 (59%) died within 48 hours, prior to susceptibility results returning.

The univariate and multivariate logistic regression analyses for risk factors associated with 30-day mortality are shown in Table 4. In the multivariate logistic regression model, mechanical ventilation and renal dysfunction were significantly associated with an increased risk of mortality. Female sex and receipt of appropriate antibiotics were associated with a significantly decreased risk of mortality. Using 14-day mortality instead as the outcome did not change the multivariate model (data not shown). The Kaplan-Meier survival curves (Figure 1) demonstrated a significant difference at 30 days, with patients with MDR *A. baumannii* bacteremia having a decreased probability of survival in comparison to patients with susceptible *A. baumannii* bacteremia (log-rank test, $p < 0.01$) and patients with non-*baumannii* ACB complex bacteremia (log-rank test, $p < 0.01$). Patients with susceptible *A. baumannii* bacteremia did not have improved survival compared with patients with non-*baumannii* ACB complex bacteremia (log-rank test, $p = 0.56$).

Discussion

Infections due to *A. baumannii* are common in critically ill patients, are difficult to treat due to multidrug resistance, and are associated with high attributable mortality, particularly in the ICU.^{4,33} Earlier studies examining mortality in patients with *Acinetobacter* bacteremia did not differentiate among members of the ACB complex.^{33–36} More recent studies using sequence-based methods to identify *Acinetobacter* genospecies have demonstrated that the clinical characteristics of infected patients, antimicrobial susceptibility patterns, and clinical outcomes vary significantly for *A. baumannii* vs. non-*baumannii* ACB complex bacteremia.^{10,11,13,15}

In this study, we used the *rpoB* gene sequence extracted from the whole genome sequence to demonstrate that 21% of blood cultures identified as ACB complex at a single tertiary care academic medical center in the U.S. are due to non-*baumannii* species. This is similar to the distribution reported in a lab-based study of *Acinetobacter* blood isolates from Taiwan.¹⁷ However, other studies from Taiwan and the U.S. found *A. nosocomialis* to be more common than *A. pittii* among non-*baumannii* ACB complex blood isolates.^{11,14,15} Most of these prior studies relied on 16S rRNA ITS sequencing to differentiate among *Acinetobacter* genospecies and, therefore, may not have accurately identified isolates to the genospecies level.^{10,11,13,15,16} An advantage of our study was the use of *rpoB* housekeeping gene sequence analysis for speciation. Housekeeping gene sequence analysis captures faster gene evolution rates and may more accurately differentiate among closely related *Acinetobacter* species.^{18,24} In a recent study comparing genotypic methods for speciation of a collection of 167 *Acinetobacter* clinical isolates, the accuracy of *rpoB* gene sequencing was 98.2%.³⁷ This was superior to 16S rRNA gene sequencing (93.4%), *gyrB* multiplex PCR (77.2%) and the VITEK2 system (35.9%).³⁷ Larger surveillance studies using *rpoB* gene sequence analysis or whole genome sequencing are needed to delineate further the factors influencing the global genospecies distribution of ACB complex blood isolates.

The clinical characteristics of our patients suggest that *A. baumannii* bacteremia may be more likely to occur in critically ill patients with multiple comorbidities, extensive prior antibiotic exposure, and requiring mechanical ventilation. Other studies have found similar associations.^{12,16} We also identified higher rates of antimicrobial resistance among *A.*

baumannii isolates for all antimicrobials tested except colistin. The contrast was particularly evident for ciprofloxacin, with 90% susceptibility noted in non-*baumannii* ACB complex isolates compared with 18% in *A. baumannii*. This particular discrepancy in fluoroquinolone susceptibility has also been observed in other studies.^{11,17} Furthermore, a recent study of tigecycline *in vitro* antimicrobial susceptibility testing demonstrated significantly elevated MICs for *A. baumannii* with the Etest compared to broth microdilution.³⁸ Therefore, the low rate of tigecycline susceptibility among our isolates may have been influenced by the use of Etest for susceptibility testing.

It is also important to note that a significant proportion of our patients had polymicrobial infection. Polymicrobial infection is commonly associated with *Acinetobacter* bacteremia. In a large study of > 10,000 patients with *Acinetobacter* bacteremia at U.S. hospitals, 36% had polymicrobial bloodstream infection.³⁹ This study found no differences in clinical outcomes between patients with monomicrobial and polymicrobial bloodstream infection. Lee et al. describe similar results in their study of ACB complex bacteremia, with 40.2% of *A. baumannii*, 32.5% of *A. pittii*, and 28.6% of *A. nosocomialis* bacteremia being polymicrobial.¹⁵ Similar to our study, this study did not find a statistically significant difference among the genospecies in the proportion of infections that were polymicrobial. Furthermore, a study examining the impact of carbapenem resistance and receipt of active antibiotic therapy on *A. baumannii* bacteremia failed to identify a statistically significant difference in the proportion of polymicrobial bacteremia between carbapenem-resistant and carbapenem-susceptible *A. baumannii*.⁴⁰ These studies demonstrate that polymicrobial infection is unlikely to have a significant influence on clinical outcomes. Furthermore, any possible influence is likely to be similar in both *A. baumannii* and non-*baumannii* infections and both susceptible and multidrug resistant infections.

In our study, we demonstrated that MDR *A. baumannii* bloodstream infection is associated with worse outcomes compared to both susceptible *A. baumannii* and non-*baumannii* ACB complex bloodstream infection. There is no difference in outcomes between susceptible *A. baumannii* and susceptible non-*baumannii* ACB complex infection or between MDR *A. baumannii* and MDR non-*baumannii* ACB complex infection. A study in Taiwan involving 215 patients with ACB complex bacteremia also found that genospecies was not independently associated with mortality.¹⁵ In that study, there was a trend toward worse outcomes for patients with MDR *A. baumannii*. In contrast, other studies have identified genospecies as an independent predictor of mortality. Chiang et al. found that *A. baumannii* was independently associated with 14-day mortality in a cohort of 103 patients with solid tumors and ACB complex bacteremia.¹⁰ Park et al. also found that *A. baumannii* was an independent predictor of 30-day mortality among patients with ACB complex bacteremia at a university hospital in Korea.¹² Likewise, Chusri et al. found that infection with non-*baumannii* ACB complex was associated with decreased 30-day mortality compared with carbapenem-susceptible *A. baumannii*.⁴⁴ However, the first study did not include multidrug resistance as a variable in the analysis, the second study did not directly compare MDR *A. baumannii* to susceptible *A. baumannii*, and the third study only included 18 patients with bloodstream infection out of a total of 222. Furthermore, in the last study, only 56% of patients with carbapenem-susceptible *A. baumannii* received appropriate empirical antibiotic

therapy, which may explain why these patients had worse outcomes compared to patients with non-*baumannii* ACB complex infection.⁴⁴

Multidrug resistance may be more closely associated with mortality than genospecies because it directly correlates to receipt of appropriate therapy, a more accurate predictor of clinical outcome. In a recent study from Taiwan comparing imipenem-resistant to imipenem-susceptible ACB complex bacteremia, the authors found no difference in mortality between imipenem-susceptible *A. baumannii* and non-*baumannii* ACB complex bacteremia.¹⁶ They also found that inappropriate initial therapy was the greatest risk factor for mortality.¹⁶ Likewise, in our analysis, neither MDR status nor genospecies was a significant independent predictor of mortality but receipt of appropriate antibiotic therapy was associated with a significant decreased risk of mortality. Therefore, the increased frequency of multidrug resistance and concomitant delay in appropriate therapy may explain the increased mortality seen with *A. baumannii* bacteremia rather than variation in virulence among genospecies.

Our study had a number of limitations. First, although the number of patients in our cohort was similar to prior studies, our sample size was small and included patients from a single center. We had relatively low numbers of non-*baumannii* ACB complex isolates and few cases of *A. nosocomialis* bacteremia in particular, which may have impaired our ability to identify genospecies as a significant independent predictor of mortality. Second, the retrospective design of the study may have introduced bias from unidentified confounding variables. Despite controlling for comorbidity in the multivariate analysis, the substantial number of patients with MDR *A. baumannii* who died within 48 hours of the initial culture and, thus, did not receive appropriate antibiotic therapy may have affected outcomes. Finally, we used age-adjusted Charlson co-morbidity score rather than the Acute Physiology and Chronic Health Evaluation II score for classifying severity of underlying illness. We chose the Charlson score because almost half (46%) of our patients were not in the ICU at the time of bacteremia onset. However, this score may not have accurately represented the severity of illness of ICU patients. This also may account for the lack of independent association seen between age-adjusted Charlson score and mortality in our study.

In conclusion, we found that patients with *A. baumannii* bacteremia are more likely to be critically ill and have greater comorbidities and decreased survival compared with patients with non-*baumannii* ACB complex bacteremia. The difference in mortality is likely due to higher rates of multidrug resistance in *A. baumannii* that lead to delays in receipt of appropriate therapy. The evidence from our study and others suggests that we can no longer regard patients with ACB complex bacteremia as a homogeneous group. Prior estimates of attributable mortality from *A. baumannii* infection performed without differentiating species within the ACB complex underrepresent the impact of *A. baumannii* infection on clinical outcomes. Future studies investigating rapid PCR- and sequence-based diagnostics for earlier genospecies and antimicrobial susceptibility determination of ACB complex isolates and, thus, timelier administration of targeted antimicrobial therapy are likely to show improved patient outcomes.

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Figure 1. Kaplan-Meier survival curves for 147 patients with susceptible *A. baumannii*, MDR *A. baumannii* and non-*baumannii* *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex bacteremia for 30 days post-infection.

Table 1

Clinical and demographic characteristics of patients with *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex bacteremia.

	<i>A. baumannii</i> (n = 116)	Non- <i>baumannii</i> ACB complex (n = 31)	p-value
Demographic			
Age, mean $\pm$ (SD)	53 (15)	49 (19)	0.20
Sex, female	49 (42)	19 (61)	0.07
Infection characteristics			
Source			
Catheter	78 (67)	24 (77)	0.38
Respiratory	13 (11)	1 (3)	0.30
Wound or surgical site	7 (6)	1 (3)	1.00
Intra-abdominal	8 (7)	2 (7)	1.00
Urine	2 (2)	0	1.00
Primary	8 (7)	3 (10)	0.70
Culture year			
2005–2007	46 (40)	16 (52)	0.16
2008–2010	44 (38)	10 (32)	0.36
2011–2012	26 (22)	5 (16)	0.24
Healthcare-associated	73 (63)	12 (39)	0.02
Polymicrobial	44 (38)	15 (48)	0.31
Healthcare exposures			
Central venous or arterial catheter	103 (89)	26 (84)	0.54
Mechanical ventilation	46 (40)	6 (19)	0.04
Prior antibiotic days, median (range)	5 (0–105)	0 (0–49)	0.02
ICU at onset	58 (50)	9 (29)	0.04
Clinical/laboratory			
Age-adjusted Charlson comorbidity score, median (range)	4 (0–12)	4 (0–8)	1.00
History of hematopoietic stem cell transplant	9 (8)	4 (13)	0.47
History of solid organ transplant	12 (10)	2 (7)	0.74
Current immunosuppression	61 (53)	18 (58)	0.69
Neutropenia	8 (7)	3 (10)	0.70
Diabetes mellitus	43 (37)	5 (16)	0.03
Renal dysfunction	60 (52)	9 (29)	0.03
Liver dysfunction	43 (37)	7 (23)	0.14

Data are No. (%) unless otherwise specified

ACB, *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex; SD, standard deviation; ICU, intensive care unit

Table 2

Comparison of antimicrobial susceptibilities of *Acinetobacter baumannii* and non-*baumannii* *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex isolates.

Antibiotic	No. of susceptible isolates/total no. isolates tested (%)		
	<i>A. baumannii</i>	Non- <i>baumannii</i> ACB complex	p-value
Ampicillin-sulbactam	47/105 (45)	24/26 (92)	< 0.01
Piperacillin-tazobactam	15/111 (14)	21/29 (72)	< 0.01
Imipenem	29/116 (25)	29/31 (94)	< 0.01
Cefepime	23/116 (20)	22/31 (71)	< 0.01
Ciprofloxacin	21/116 (18)	28/31 (90)	< 0.01
Amikacin	45/116 (39)	27/31 (87)	< 0.01
Tobramycin	55/116 (47)	28/31 (90)	< 0.01
Minocycline	65/110 (59)	26/29 (90)	< 0.01
Doxycycline	50/102 (49)	24/27 (89)	< 0.01
Tigecycline	16/67 (24)	17/18 (94)	< 0.01
Colistin	69/72 (96)	18/18 (100)	1.00
Multidrug resistant ^a	92/116 (79)	5/31 (16)	< 0.01

^aNumber of multidrug resistant isolates out of total (%).

Table 3

Clinical outcomes of patients with *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex bacteremia stratified by presence of multidrug resistance in *A. baumannii* isolates.

Outcome ^a	Susceptible <i>A. baumannii</i> (n = 24)	MDR <i>A. baumannii</i> (n = 92)	Non- <i>baumannii</i> ACB complex (n = 31)	p-value	
				Overall	Susceptible <i>A. baumannii</i> vs. MDR <i>A. baumannii</i> vs. non- <i>baumannii</i> ACB complex
Days to negative cultures, median (range) ^b	2 (1–5)	1 (1–7)	2 (1–6)	0.49	
Received appropriate therapy	24 (100)	63 (69)	29 (94)	< 0.01	< 0.01
Days to appropriate therapy, median (range) ^c	0.5 (0–6)	2 (0–13)	1 (0–4)	< 0.01	< 0.01
Hospital LOS postculture, median days (range)	6 (2–38)	11.5 (2–69)	5 (0–28)	0.01	0.09
30-day mortality	2 (8)	40 (44)	4 (13)	< 0.01	< 0.01
14-day mortality	2 (8)	33 (36)	4 (13)	< 0.01	0.01
Days to mortality, median (range)	10.5 (6–15)	2.5 (0–27)	1.5 (1–5)	0.40	

Data are No. (%) unless otherwise specified

ACB, *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex; MDR, multidrug resistant; LOS, length of stay

^a Statistical tests were also performed comparing outcomes between susceptible *A. baumannii* and susceptible non-*baumannii* ACB complex and also between MDR *A. baumannii* and MDR non-*baumannii* ACB complex. No significant differences were found (data not shown).

^b For 110 patients with repeat blood cultures.

^c For 117 patients receiving appropriate therapy

Table 4

Univariate and multivariate logistic regression analysis of risk factors associated with 30-day mortality in patients with *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex bacteremia.

Risk factor	Survived (n = 101)		Died (n = 46)		Univariate analysis		Multivariate analysis	
					OR (95% CI)	p-value	OR (95% CI)	p-value
Age, mean $\pm$ (SD)	51 (17)		56 (12)		1.02 (1.00–1.05)	0.06		
Sex, female	54 (54)		14 (30)		0.38 (0.18–0.80)	0.01	0.24 (0.08–0.75)	0.01
<i>A. baumannii</i>	74 (73)		42 (91)		3.83 (1.26–11.7)	0.02		
Source:								
Catheter	76 (75)		26 (57)		0.43 (0.21–0.89)	0.02		
Respiratory	3 (3)		11 (24)		10.27 (2.71–38.96)	<0.01		
Primary	10 (10)		1 (2)		0.20 (0.03–1.63)	0.13		
Healthcare-associated	46 (46)		39 (85)		6.67 (2.72–16.3)	<0.01		
Multidrug resistance	54 (54)		43 (94)		12.48 (3.63–42.85)	<0.01		
Received appropriate therapy	91 (90)		25 (54)		0.13 (0.06–0.31)	<0.01	0.13 (0.04–0.44)	<0.01
Days to appropriate therapy, median (range)	1 (0–13) ^a		1 (0–5) ^b		0.84 (0.64–1.12)	0.24		
Mechanical ventilation	16 (16)		36 (78)		19.13 (7.93–46.15)	<0.01	20.7 (6.8–62.9)	<0.01
Prior antibiotic days, median (range)	0 (0–42)		12 (0–105)		1.09 (1.05–1.13)	<0.01		
Age-adjusted Charlson comorbidity score, median (range)	3 (0–12)		5 (0–11)		1.16 (1.03–1.31)	0.01		
Current immunosuppression	46 (46)		33 (72)		3.04 (1.43–6.44)	<0.01		
Diabetes mellitus	27 (27)		21 (46)		2.3 (1.11–4.77)	0.03		
Renal dysfunction	35 (35)		34 (74)		5.34 (2.46–11.6)	<0.01	4.21 (1.46–12.1)	<0.01
Liver dysfunction	23 (23)		27 (59)		4.82 (2.28–10.19)	<0.01		

Data are No. (%) unless otherwise specified

OR, odds ratio; CI, confidence interval; SD, standard deviation; ICU, intensive care unit

^aFor the 91 survivors who received appropriate therapy

^bFor the 25 non-survivors who received appropriate therapy