2022

Treatment, Clinical Outcomes, and Predictors of Mortality among a National Cohort of Admitted Patients with Acinetobacter baumannii Infection

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Citation/Publisher Attribution

Appanel, H. J., Lopes, V. V., LaPlante, K. L. & Caffrey, A. R. (2022). Treatment, Clinical Outcomes, and Predictors of Mortality among a National Cohort of Admitted Patients with *Acinetobacter baumannii* Infection. *Antimicrobial Chemotherapy, 66*(3), e0197521. https://doi.org/10.1128/aac.01975-21
Available at: https://doi.org/10.1128/aac.01975-21

Treatment, Clinical Outcomes, and Predictors of Mortality among a National Cohort of Admitted Patients with Acinetobacter baumannii Infection

Title:

Treatment, clinical outcomes, and predictors of mortality among a national cohort of admitted patients with *Acinetobacter baumannii* infection

Running title:

Acinetobacter baumannii infection mortality predictors

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Word Count: 2,471

Author Contributions:

Conception and design of the study: ARC, HA, KL

Data generation: HA, ARC, VL

Analysis and interpretation of the data: HA, ARC, KL

Preparation or critical revision of the manuscript: HA, ARC, KL

Potential conflicts of interest disclosure:

Haley Appaneal has received research funding from Shinogi.

Kerry LaPlante has received research funding or acted as a scientific advisor for Merck, Parateck, Pfizer, Spero, and Shinogi.

Aisling Caffrey has received research funding from Gilead, Merck, Pfizer, and Shionogi, and has received speaking honoraria from Merck.

No other financial disclosures.

Funding:

This work was funded, in part, by Shinogi, Inc.

Acknowledgements:

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs. This material is based upon work supported, in part, by the Office of Research and Development, Department of Veterans Affairs.

Compliance with ethics guidelines:

The study was approved by the Institutional Review Board (IRB) and the Research and Development (R&D) Committee of the Providence Veterans Affairs Medical Center prior to initiation with a waiver of the informed consent process. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication:

Not applicable

Data availability:

The de-identified datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request and approval of the Providence Veterans Affairs Medical Center IRB.

ABSTRACT:

WORD COUNT: 246

Objectives: To analyze treatment, clinical outcomes, and predictors of mortality in hospitalized patients with *Acinetobacter baumannii* infection.

Methods: Retrospective cohort study of inpatients with *A. baumannii* cultures and treatment from 2010-2019. Patients who died during admission were compared to those who survived to identify predictors of inpatient mortality, using multivariable unconditional logistic regression models.

Results: We identified 4,599 inpatients with *A. baumannii* infection; 13.6% died during admission. Fluoroquinolones (26.8%), piperacillin/tazobactam (24%) and carbapenems (15.6%) were used for treatment. Tigecycline (3%) and polymyxins (3.7%) were not used often. Predictors of inpatient mortality included current acute respiratory failure (adjusted odds ratio [aOR] 3.94), shock (aOR 3.05), and acute renal failure (aOR 2.01); blood (aOR 1.94) and respiratory (aOR 1.64) infectious source; multidrug-resistant *A. baumannii* (MDRAB) infection (aOR 1.66); liver disease (aOR 2.15); and inadequate initial treatment (aOR 1.30). Inpatient mortality was higher in those with MDRAB vs. non-MDRAB (aOR 1.61) and in those with CRAB vs. non-CRAB infection (aOR 1.68). Length of stay >10 days was higher among those with MDRAB vs. non-MDRAB (aOR 1.25) and in those with CRAB vs. non-CRAB infection (aOR 1.31).

Conclusions: In our national cohort of inpatients with *A. baumannii* infection, clinical outcomes were worse among those with MDRAB and/or CRAB infection. Predictors of inpatient mortality included several current conditions associated with severity, infectious source, underlying illness, and inappropriate treatment. Our study may assist healthcare providers in the early identification of admitted patients with *A. baumannii* infection who are at higher risk of death.

WORD COUNT: 2,840; reference count 25

INTRODUCTION

Acinetobacter baumannii, primarily a nosocomial pathogen, is one of the most antibiotic resistant pathogens in clinical medicine.(1) Estimates of mortality rates among patients with *A. baumannii* infections have ranged from 26.0% to 55.7%, with estimated attributable mortality rates between 8.4% and 36.5%.(2) While bacteremia and pneumonia are the most severe infections caused by *A. baumannii*, this organism can cause a variety of other serious infections including urinary tract infections, skin and soft tissue infections, wound infections, osteomyelitis, and meningitis.(1) *A. baumannii* infections have become increasingly difficult to treat due to the emergence of multidrug-resistant *A. baumannii* (MDRAB) and carbapenem-resistant *A. baumannii* (CRAB) strains.(3) The high prevalence of MDRAB and/or CRAB strains presents a real challenge for clinical treatment, as resistance is associated with inappropriate initial therapy and worse outcomes for patients with *A. baumannii* infection, including higher mortality.(3, 4)

In addition to resistance, identification of other risk factors for mortality could be helpful in early identification of patients at higher risk of death and improving clinical outcomes associated with *A. baumannii* infections. Previous studies have already identified several risk factors for mortality among hospitalized patients with *A. baumannii* infection, such as intensive care unit (ICU) stay, older age, renal failure, and septic shock. However, these studies were limited to patients with single-system infections, generally bacteremia or pneumonia, were small, older, single center studies, which did not control for differences in antibiotic treatment.(5-7) As such the aims of this work were to identify predictors of inpatient mortality while controlling for antibiotic treatment and to evaluate the impact of resistance on clinical outcomes in a national cohort of hospitalized patients with *A. baumannii* infection.

METHODS

The national VA datasets used for this work included inpatient admissions, inpatient and outpatient care, diagnoses, procedures, vital status, microbiology, and pharmacy.

The retrospective cohort study selected a cohort of adult inpatients (age ≥ 18 years) admitted to VA hospitals nationally with positive *A. baumannii* cultures from any infectious source (blood, urine, respiratory, skin and tissue, and other) collected between January 1, 2010 and April 30, 2019. Further inclusion criteria consisted of antibiotic treatment with activity against *A. baumannii* within 2 days of culture collection, treatment duration of 2 days or more, index culture and susceptibility report completion time ten days or less, and the first qualifying admission meeting these criteria during the study period. In the case of multiple positive *A. baumannii* cultures during the admission, the first culture was considered the index culture.

Clinical characteristics of our cohort were evaluated, including demographics, current conditions and medical history, and prior antibiotic and healthcare exposures. Current conditions, including infections and other acute events, were identified using International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or 10) diagnosis and procedure codes during the admission. Medical history was identified using ICD-9/10 codes in the year prior to the admission. Co-infections were defined as cultures positive for other organisms assessed from three days prior through the day of *A. baumannii* collection. Antibiotic treatments were evaluated by antibiotic agent and class. Inadequate initial treatment was defined as lack of receipt of at least one treatment in which the index *A. baumannii* isolate demonstrated susceptibility to within 4 days after culture collection.

MDRAB infection was defined as *A. baumannii* infection due to an isolate that demonstrated non-susceptibility (intermediate or resistant) to at least 1 drug in at least 3 antibiotic classes (extended-

spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, and ampicillin/sulbactam).(8) Isolates not meeting the definition of MDRAB, either due to susceptibility or absence of susceptibility testing against one of more antibiotic classes, were defined as non-MDRAB. CRAB infection was defined as *A. baumannii* infection due to an isolate that demonstrated non-susceptibility to at least 1 carbapenem (imipenem, meropenem, or doripenem).(8) Isolates not meeting the definition of CRAB, either due to susceptibility or absence of susceptibility testing against carbapenems, were defined as non-CRAB.

Clinical outcomes evaluated included all-cause inpatient mortality during the admission and 30-day mortality from culture collection, length of stay greater than 10 days, reinfection defined as a subsequent positive *A. baumannii* culture within 30 days of discharge, and readmission to a VA hospital within 30 days of discharge.

Clinical characteristics and antibiotic treatment were compared between patients who died during the admission and those who survived. Categorical variables were compared using chi-square or Fisher's exact tests where appropriate, means were compared using t-tests, and medians were compared using non-parametric Wilcoxon tests. Backwards, manual, stepwise unconditional logistic regression (initial selection p-value <0.1, retained in model p-value <0.05) was used to identify characteristics that were predictive of inpatient mortality while controlling for confounding, which included imbalances in antibiotic treatment, time to culture collection, and year of treatment, between survivors and non-survivors and other factors protective against mortality.(9) Potential predictors were selected *a priori* and were based on previously described predictors of poor outcomes in patients with *A. baumannii* infection.(4, 10) Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated for independent predictors of inpatient mortality (aORs

> 1.0). Absence of collinearity between the variables in the final model was assessed from tolerance and variance inflation.(9)

We also calculated aORs and 95% CIs for resistance (MDRAB vs. non-MDRAB, and CRAB vs. non-CRAB) and each of the aforementioned clinical outcomes. Confounders significantly associated with both resistance and clinical outcomes were controlled for in the adjusted models (backwards, automatic, stepwise unconditional logistic regression, initial selection p-value <0.1, retained in model p-value <0.05). For our analysis assessing the impact of resistance on clinical outcomes, we excluded patients without MDR or carbapenem susceptibility results. We conducted subgroup analyses by culture source (for blood cultures and respiratory cultures), and monomicrobial *Acinetobacter baumannii* cultures.

RESULTS

This study identified a cohort of 4,599 hospitalized patients treated for an *A. baumannii* infection. The infectious source of their *A. baumannii* infection was most commonly urine (28.5%, n=1,313), followed by skin and soft tissue (25.4%, n=1,166) and respiratory (24.9%, n=1,146) sources. The overall inpatient mortality rate was 13.6% (n=626). Demographics and clinical characteristics are presented in Table 1. Those who died during admission were significantly older (mean age 70.9 [± 11.2] vs. 66.7 [±12.1] years) and more likely to be treated by intensive care (43.5% vs. 19.4%) than those who survived. Those who died were significantly more likely to have MDRAB (65.3% vs. 34.1%) and/or CRAB (45.5% vs. 21.9%) infections than those who survived, and less likely to have coinfections with other organisms (56.2% vs. 65.5%).

Current acute conditions and medical history are shown in Table 2. Those who died during admission were significantly more likely to have current acute respiratory failure (75.7% vs. 23.6%), shock (44.2% vs. 7.6%), and acute renal failure (60.1% vs. 29.2%) than those who

survived the admission. Those who died were also significantly more likely to have a medical history of liver disease (9.1% vs. 6.7%) and cancer or malignancy (29.7% vs. 26.2%) than those who survived. The median Charlson score in those who died was 4 (interquartile [IQR] range 2-6) as compared to 3 (IQR 1-5) in those that survived.

Antibiotic treatment exposures for the study cohort are shown in Table 3. Fluoroquinolones (26.8%) and piperacillin/tazobactam (24%) were the most used antibiotics. Carbapenems were used in 15.6% of patients. Most carbapenem usage was as monotherapy (74.0%, n=530/716), as was fluroquinolone (63.6%, 783/1,232) and piperacillin/tazobactam usage (77.0%, n=849/1,102). Combination therapy was used in 18.4% of patients. Only 3% of patients were treated with tigecycline (53.3%, n=73/137 as combination therapy) and 3.7% with a polymyxin (55.0%, n=93/169 as combination therapy). Those who died during were significantly more likely to be treated with tigecycline (7.2% vs. 2.3%), a carbapenem (32.9% vs. 12.8%), or a polymyxin (12.9% vs. 2.2%) than those who survived. Inadequate initial treatment was significantly more common in those who died as compared to those who survived (59.9% vs. 46.5%).

Several (n=12) predictors of inpatient mortality (Table 4), controlling for antibiotic treatment, time to culture from admission, year of treatment, and factors associated with survival, were identified including: presence of current acute respiratory failure (aOR 3.94; 95% CI, 3.07-5.05), shock (aOR 3.05; 95% CI, 2.36-3.94), and acute renal failure (aOR 2.01; 95% CI, 1.62-2.49); blood (aOR 1.94; 95% CI, 1.40-2.69) and respiratory (aOR 1.64; 95% CI, 1.29-2.09) infectious source; MDRAB infection (aOR 1.66; 95% CI, 1.30-2.12); medical history of liver disease (aOR 2.15, 95% CI, 1.46-3.17) and cancer or malignancy (aOR 1.40; 95% CI, 1.11-1.76); and inadequate initial treatment (aOR 1.30; 95% CI, 1.04-1.64). Results of subgroup analyses can be found in the supplemental material. Current acute respiratory failure, shock, and acute renal failure, and

MDRAB infection remained significant predictors of inpatient mortality in all subgroups assessed (Table S1).

Clinical outcomes can be found in Table 5. Most clinical outcomes were significantly worse for those with MDRAB or CRAB infection, including inpatient mortality (MDRAB 23.1% vs. non-MDRAB 7.7%; CRAB 24.7% vs. non-CRAB 8.5%) and length of stay greater than 10 days (MDRAB 68.7% vs. non-MDRAB 42.5%; CRAB 71.7% vs. non-CRAB 44.8%). Inpatient mortality was significantly higher in those with MDRAB vs. non-MDRAB (aOR 1.61; 95% CI 1.26-2.06) and in those with CRAB vs. non-CRAB infection (aOR 1.68; 95% CI 1.31-2.17), and the odds of a longer length of stay (>10 days) was significantly higher among those with MDRAB vs. non-MDRAB (aOR 1.25; 95% CI 1.03-1.52) and in those with CRAB vs. non-CRAB infection (aOR 1.31; 95% CI 1.04-1.65). Results of subgroup analyses were generally similar to the overall cohort Table S2). However, the odds of a longer length of stay (>10 days) was significantly lower among those with MDRAB vs. non-MDRAB (aOR 0.37; 95% CI 0.19-0.73) and among those with CRAB vs. non-CRAB infection (aOR 0.37; 95% CI 0.16-0.86) in the subgroup of patients with blood source infections and not significantly different for MDRAB or CRAB infections in the subgroup of patients with respiratory source infections.

DISCUSSION

To our knowledge, this is the first multicenter study to identify predictors of inpatient mortality associated with all types of *A. baumannii* infections. This study demonstrated poor outcomes for hospitalized patients with *A. baumannii* infection, with significantly worse outcomes among those with MDRAB and/or CRAB infection.

The inpatient mortality rate we observed (13.6%) was similar to several previous studies which have described inpatient mortality rates of 12.7% and 17.6%.(3, 11) Similar to previous work, we

identified several predictors of mortality related to the severity of infection, including septicemia, shock, acute respiratory failure, and acute renal failure.(7, 12) These conditions are all signs of severe infection and resultant multiple organ dysfunction that are often present in critically ill patients and contribute to poor outcomes including mortality.(12) We also identified that current anemia was an independent predictor of mortality, in contrast to previous findings.(10) As patients with anemia have low hemoglobin levels and may have disrupted transportation of oxygen to organ systems leading to hypoxia, anemia may exacerbate multiple organ dysfunction seen in critically ill patients thus contributing to excess mortality.(13) Additionally, in a previous study of 175 hospitals in the United States, anemia was more common among patients with MDRAB vs non-MDRAB pneumonia and sepsis (50.6% vs. 38.5%, $p<0.001$); and hospital mortality was higher in those with MDRAB.(14) Finally, our results may be related to the need for red blood cell transfusion in patients with severe anemia. Previous work demonstrated that red blood cell transfusion was a strong independent predictor of in-hospital mortality among patients with MDRAB ventilator associated pneumonia.(15)

We also found that that underlying medical conditions (liver disease and cancer) and increasing age were predictors of mortality, which is consistent with previous findings.(12, 16-18) Previously, among two seprate cohorts of hospitalized patients with *A. baumannii* bacteremia (n=188 and n=122), malignancy was predictive of mortality.(18, 19) A meta-analysis of 19 observational studies found that liver disease was an important factor associated with mortality in patients infected with CRAB.(12)

Blood source and respiratory sources of infection were also predictive of mortality in our cohort. These results are expected as pneumonia and bacteremia are generally associated with more serious *A. baumannii* disease and worse patient outcomes than other infection types.(1) Previous work among hospitalized patients with *A. baumannii* also demonstrated that blood

source of *A. baumannii* infection was an independent predictor of mortality (OR, 4.64, 95% CI, 1.26–17.06).(10) Bacteremia is an important and common cause of death. Previous work has demonstrated that among patients with ventilator associated pneumonia (VAP) *A. baumannii*, the mortality rate was higher in patients with VAP and bacteremia as compared to those with nonbacteremic VAP (32.4% vs 9.6%, P<0.005).(20) Pneumonia is also an important cause of death. Previously, recovery of *A. baumannii* from the respiratory tract was identified as major risk factor related to mortality among patients in the ICU with nosocomial *A. baumannii* infections.(21) Among 338 patients with nosocomial *A. baumannii* bacteremia, bacteremia occurring after severe pneumonia was an independent risk factor mortality.(16)

As with several previous studies, we found that MDRAB infection was an independent risk factor for mortality. Infection with MDRAB often leads to high treatment failure and worse outcomes than susceptible *A. baumannii* infection. A previous retrospective, matched cohort study in 2 hospitals found that after controlling for severity of illness and underlying disease, MDRAB was independently associated with increased hospital and intensive care unit length of stay as compared to susceptible MDRAB.(3) The association between MDRAB infection and worse clinical outcomes is likely related to increased probability for inappropriate initial antibiotic therapy, delay to active antibiotics, and resultant increased severity of disease and increased risk for treatment failure, rather than enhanced virulence of the organism.(17, 22-24) When controlling for treatment and severity, MDRAB was still an independent predictor of mortality in our study. In prior work, those with MDRAB were fivefold more likely to receive inappropriate empiric treatment than those with non-MDRAB pneumonia or sepsis, and inappropriate empiric treatment nearly doubled in-hospital mortality.(14)

As expected, clinical outcomes were significantly worse among those with MDRAB and CRAB as compared to susceptible *A. baumannii* infections. Similarly, previous work has demonstrated that

resistant *A. baumannii* infections are associated with higher mortality and morbidity, including increased length of hospital stay, readmission rates, and reinfection rates.(3) All-cause readmissions and readmissions during which MDR organisms are isolated are common among patients with infections due to MDR pathogens.(25) As with MDRAB, poor outcomes among those with CRAB are likely related to inappropriate initial antibiotic therapy. A systematic review of observational studies that included over 2,500 patient with CRAB and susceptible *A. baumannii* infection found that CRAB was associated with a greater risk of mortality (OR 2.22, 95% CI 1.66-2.98) and those with CRAB were more likely to receive inappropriate initial antibiotic therapy.(4)

There are limitations inherent in the present work. Clinical signs and symptoms of infection were not assessed, and thus some of the *A. baumannii* cultures we captured may have represented colonization rather than true infection. However, only patients in which antibiotics with activity against *A. baumannii* were used were included and patients had to be treated for a minimum duration of at least 2 days. Additionally, several infection diagnoses for which *A. baumannii* is known to cause were common during the admission, including bacterial infection of an unspecified site (which includes bacteremia) 44.9%, pneumonia 31.9%, and urinary tract infection 42.2%. Moreover, results were similar among the subgroups of patients with blood source and respiratory source infections. To capture the full spectrum of antibiotic treatment among hospitalized patients with *A. baumannii* infection, patients who had positive cultures for other organisms (coinfections) were not excluded, thus some of the antibiotic treatment captured may have been targeting other non-*A. baumannii* organisms and/or infections. Reassuringly, results were similar among the subgroup of patients with monomicrobial *A. baumannii* infections. For clinical outcomes, only readmissions and reinfections that were treated within the VA healthcare system were captured. Additionally, all outcomes assessed were all cause and not necessarily *A. baumannii* infection related. In our predictive analysis, we considered several risk factors for poor outcomes in patients with *A. baumannii* infection that have been previously described, however there may be other

known and unknown risk factors that were not included in our study. The generalizability of this study may be limited to the patients admitted to VA hospitals.

In our national cohort of hospitalized patients with *A. baumannii* infection, 13.6% of patients died during admission and clinical outcomes were worse for those with MDRAB or CRAB infection. While most of the predictors we identified have been previously identified (separately or together with other identified predictors) in various other studies of patients with *A. baumannii* infection, mostly bacteremia and pneumonia, these studies did not control for differences in antibiotic treatments. Additionally, our study is the first to identify this full list of predictors of inpatient morality among hospitalized patients with all types of *A. baumannii* infection and the first to identify anemia as an independent predictor. Controlling for antibiotic treatment, the predictors of inpatient morality we identified included current conditions, infectious source, underlying illness, and MDRAB infection. Our study may assist health care providers in the early identification of admitted patients with *A. baumannii* infection who are at higher risk of death.

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Table 1: Baseline demographics and clinical characteristics among hospitalized patients with *Acinetobacter baumannii* infection

Demographics and clinical characteristics	All hospitalized patients with *A. baumannii* infection N = 4,599	Inpatient mortality N=626 (13.6)	Inpatient survival N=3,973 (86.4)	P
Age, years, mean (standard deviation)	67.3 (12.1)	70.9 (11.2)	66.7 (12.1)	<0.001
Male	4,484 (97.5)	616 (98.4)	3,868 (97.4)	0.120
White	3,008 (65.4)	406 (64.9)	2,602 (65.5)	0.756
Hispanic or Latino	448 (9.7)	111 (17.7)	337 (8.5)	<0.001
Married	1,811 (39.4)	285 (45.5)	1,526 (38.4)	0.001
Community admission	1,851 (40.2)	182 (29.1)	1,669 (42)	<0.001
Intensive care unit treatment specialty	1,041 (22.6)	272 (43.5)	769 (19.4)	<0.001
Prior antibiotic and healthcare exposures, 30 days prior to admission				
Antibiotic exposure	1,761 (38.3)	219 (35)	1,542 (38.8)	0.067
Hospital exposure	962 (20.9)	141 (22.5)	821 (20.7)	0.288
Intensive care unit exposure	244 (5.3)	43 (6.9)	201 (5.1)	0.060
Nursing home exposure	100 (2.2)	16 (2.6)	84 (2.1)	0.481

Multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection[1]	1,762 (38.3)	409 (65.3)	1,353 (34.1)	<0.001
Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection[2]	1,155 (25.1)	285 (45.5)	870 (21.9)	<0.001
Resistance phenotype of index *Acinetobacter baumannii* isolate				
Aminoglycoside[3]	1,440 (31.3%)	345 (55.1)	1095 (27.6)	<0.001
Ampicillin/sulbactam	867 (18.9%)	219 (35.0)	648 (16.3)	<0.001
Anti-pseudomonal penicillins + β-lactamase inhibitors[4]	1,268 (27.6%)	243 (38.8)	1,025 (25.8)	<0.001
Extended-spectrum cephalosporins[5]	3,252 (70.7%)	505 (80.7)	2,747 (69.1)	<0.001
Fluoroquinolones[6]	1,988 (43.2%)	437 (69.8)	1,551 (39.0)	<0.001
Sulfamethoxazole/trimethoprim	1,462 (31.8%)	314 (50.2)	1,148 (28.9)	<0.001
Culture characteristics				
Time to culture from admission, days, median (interquartile range)	1 (0-7)	8 (1-27)	1 (0-5)	<0.001
Time to culture report completion, days, median (interquartile range)	4 (3-5)	4 (3-5)	4 (3-5)	0.003
Infectious source[7]				
Blood	534 (11.6)	99 (15.8)	435 (10.9)	<0.001
Bone and joint	204 (4.4)	20 (3.2)	184 (4.6)	0.105

Respiratory	1,146 (24.9)	339 (54.2)	807 (20.3)	<0.001
Skin and tissue	1,166 (25.4)	71 (11.3)	1,095 (27.6)	<0.001
Urine	1,313 (28.5)	87 (13.9)	1,226 (30.9)	<0.001
Other	338 (7.3)	38 (6.1)	300 (7.6)	0.187
Coinfection[8]	2,953 (64.2)	352 (56.2)	2,601 (65.5)	<0.001
Citrobacter	81 (1.8)	15 (2.4)	66 (1.7)	0.194
Enterobacter	246 (5.3)	23 (3.7)	223 (5.6)	0.045
Enterococcus	857 (18.6)	88 (14.1)	769 (19.4)	0.002
Escherichia coli	466 (10.1)	57 (9.1)	409 (10.3)	0.360
Klebsiella	455 (9.9)	79 (12.6)	376 (9.5)	0.014
Morganella morganii	68 (1.5)	8 (1.3)	60 (1.5)	0.655
Proteus mirabilis	340 (7.4)	47 (7.5)	293 (7.4)	0.906
Pseudomonas aeruginosa	554 (12)	87 (13.9)	467 (11.8)	0.126
Serratia marcescens	60 (1.3)	15 (2.4)	45 (1.1)	0.010
Staphylococcus aureus	959 (20.9)	109 (17.4)	850 (21.4)	0.023
Streptococcus pneumoniae	10 (0.2)	0 (0)	10 (0.3)	0.209
Other	761 (16.5)	76 (12.1)	685 (17.2)	0.001

Data are n (%), unless otherwise indicated. Categorical variables were compared using chi-square or Fisher's exact tests where appropriate, means were compared using t-tests, and medians were compared using non-parametric Wilcoxon tests.

[1]Multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection was defined as infection due to a MDR *A. baumannii* strain as compared to infection due to a non-MDR *A. baumannii* strain, either due to susceptibility or absence of susceptibility testing.

[2]Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection was defined as infection due to a carbapenem-resistant *A. baumannii* strain as compared to infection due to a non-

carbapenem-susceptible *A. baumannii* strain, either due to susceptibility or absence of susceptibility testing.

[3]Aminoglycosides (amikacin, gentamicin, tobramycin).

[4]Anti-pseudomonal penicillins + β-lactamase inhibitors (piperacillin/tazobactam, clavulanate/ticarcillin).

[5]Extended-spectrum cephalosporins (cefepime, ceftazidime, cefotaxime, ceftriaxone).

[6]Fluoroquinolones (ciprofloxacin, levofloxacin).

[7]Counts and percentages are not mutually exclusive as patients may have had multiple positive culture sites positive for *Acinetobacter baumannii*.

[8]Co-infections were assessed from three days prior through the day of *Acinetobacter baumannii* culture collection. Counts and percentages are not mutually exclusive as patients may have had multiple positive organisms in the same culture site, or multiple positive culture sites with multiple organisms.

Table 2: Current conditions and medical history among hospitalized patients with *Acinetobacter baumannii* infection

	All hospitalized patients with *A. baumannii* infection N = 4,599	Inpatient mortality N=626 (13.6)	Inpatient survival N=3,973 (86.4)	P
Current conditions Anemia	1,711 (37.2)	283 (45.2)	1,428 (35.9)	<0.001
Acute renal failure	1,535 (33.4)	376 (60.1)	1,159 (29.2)	<0.001
Acute respiratory failure	1,411 (30.7)	474 (75.7)	937 (23.6)	<0.001
Adverse effects of medical care	575 (12.5)	61 (9.7)	514 (12.9)	0.025
Bacterial infection, unspecified site	2,064 (44.9)	215 (34.3)	1,849 (46.5)	<0.001
Complication of surgical or medical procedure	993 (21.6)	167 (26.7)	826 (20.8)	<0.001
Complication of device, implant, or graft	656 (14.3)	96 (15.3)	560 (14.1)	0.410
Fever	420 (9.1)	62 (9.9)	358 (9)	0.471
Osteomyelitis and infective arthritis	888 (19.3)	88 (14.1)	800 (20.1)	<0.001
Pneumonia	1,443 (31.4)	387 (61.8)	1,056 (26.6)	<0.001
Septicemia	1,828 (39.7)	452 (72.2)	1,376 (34.6)	<0.001

Shock	580 (12.6)	277 (44.2)	303 (7.6)	<0.001
Skin and subcutaneous infection	1,092 (23.7)	91 (14.5)	1,001 (25.2)	<0.001
Urinary tract infection	1,940 (42.2)	263 (42)	1,677 (42.2)	0.926
Wound	366 (8.0)	42 (6.7)	324 (8.2)	0.214
Medical history Atherosclerosis	1,377 (29.9)	205 (32.7)	1,172 (29.5)	0.099
Cancer or malignancy	1,225 (26.6)	186 (29.7)	1,039 (26.2)	0.061
Cerebrovascular disease	531 (11.5)	86 (13.7)	445 (11.2)	0.065
Chronic kidney disease	1,145 (24.9)	199 (31.8)	946 (23.8)	<0.001
Chronic obstructive pulmonary disease	1,483 (32.2)	232 (37.1)	1,251 (31.5)	0.006
Congestive heart failure	1,057 (23.0)	186 (29.7)	871 (21.9)	<0.001
Diabetes mellitus	2,111 (45.9)	285 (45.5)	1,826 (46)	0.840
Hypertension	3,328 (72.4)	463 (74)	2,865 (72.1)	0.336
Immunocompromised	43 (0.9)	9 (1.4)	34 (0.9)	0.160
Liver disease	322 (7)	57 (9.1)	265 (6.7)	0.027
Transplant	39 (0.8)	10 (1.6)	29 (0.7)	0.028
Charlson score, median (interquartile range)	3 (2-6)	4 (2-6)	3 (1-5)	<0.001
Elixhauser score, median (interquartile range)	5 (3-7)	6 (3-7)	5 (3-7)	<0.001

Data are n (%), unless otherwise indicated. Categorical variables were compared using chi-square or Fisher's exact tests where appropriate, medians were compared using non-parametric Wilcoxon tests.

Current conditions, including infections and other acute events, were identified using International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or 10) diagnosis and procedure codes during the admission. Medical history was identified using ICD-9/10 codes in the year prior to the admission.

Table 3: Antibiotic exposures among hospitalized patients with *Acinetobacter baumannii* infection

Antibiotic treatments	All hospitalized patients with an *A. baumannii* infection N = 4,599	Inpatient mortality N=626 (13.6)	Inpatient survival N=3,973 (86.4)	P
Inadequate initial treatment[1]	2,221 (48.3)	375 (59.9)	1,846 (46.5)	<0.001
Amikacin	56 (1.2)	11 (1.8)	45 (1.1)	0.185
Ampicillin/sulbactam	380 (8.3)	44 (7)	336 (8.5)	0.228
Cefepime	462 (10)	77 (12.3)	385 (9.7)	0.044
Ceftazidime	104 (2.3)	21 (3.4)	83 (2.1)	0.048
Ceftriaxone	418 (9.1)	23 (3.7)	395 (9.9)	<0.001
Ciprofloxacin	814 (17.7)	44 (7)	770 (19.4)	<0.001
Colistin	87 (1.9)	37 (5.9)	50 (1.3)	<0.001
Doripenem	28 (0.6)	8 (1.3)	20 (0.5)	0.021
Doxycycline	163 (3.5)	4 (0.6)	159 (4)	<0.001
Gentamicin	78 (1.7)	15 (2.4)	63 (1.6)	0.144
Imipenem	345 (7.5)	115 (18.4)	230 (5.8)	<0.001
Levofloxacin	431 (9.4)	30 (4.8)	401 (10.1)	<0.001
Meropenem	346 (7.5)	84 (13.4)	262 (6.6)	<0.001
Minocycline	72 (1.6)	3 (0.5)	69 (1.7)	0.019
Piperacillin/tazobactam	1,102 (24)	155 (24.8)	947 (23.8)	0.615
Polymyxin B	84 (1.8)	46 (7.3)	38 (1)	<0.001

Sulfamethoxazole/trimethoprim	368 (8)	18 (2.9)	350 (8.8)	<0.001
Tigecycline	137 (3)	45 (7.2)	92 (2.3)	<0.001
Tobramycin	52 (1.1)	12 (1.9)	40 (1)	0.045
Antibiotic classes				
Aminoglycoside[2]	186 (4)	38 (6.1)	148 (3.7)	0.006
Carbapenems[3]	716 (15.6)	206 (32.9)	510 (12.8)	<0.001
Extended-spectrum cephalosporins[4]	980 (21.3)	120 (19.2)	860 (21.6)	0.160
Fluoroquinolones[5]	1232 (26.8)	73 (11.7)	1,159 (29.2)	<0.001
Anti-pseudomonal penicillins + β-lactamase inhibitors[6]	1,106 (24)	156 (24.9)	950 (23.9)	0.583
Polymyxins[7]	169 (3.7)	81 (12.9)	88 (2.2)	<0.001
Tetracyclines[8]	235 (5.1)	7 (1.1)	228 (5.7)	<0.001

Data are n (%). Categorical variables were compared using chi-square or Fisher's exact tests where appropriate.

Assessed antibiotic treatment with activity against *A. baumannii,* which included amikacin, ampicillin/sulbactam, cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, clavulanate/ticarcillin, colistin, doripenem, doxycycline, gentamicin, imipenem, levofloxacin, meropenem, minocycline, piperacillin/tazobactam, polymyxin B, sulfamethoxazole/trimethoprim, tetracycline, tigecycline and tobramycin.

[1]Inadequate initial treatment was assessed from culture collection of the *A. baumannii* isolate until the 4th day after culture and defined as lack of receipt of at least one antibiotic with susceptibility.

[2]Aminoglycosides (amikacin, gentamicin, tobramycin).

[3]Carbapenems (imipenem, meropenem, doripenem).

[4]Extended-spectrum cephalosporins (cefepime, ceftazidime, cefotaxime, ceftriaxone).

[5]Fluoroquinolones (ciprofloxacin, levofloxacin).

[6]Anti-pseudomonal penicillins + β-lactamase inhibitors (piperacillin/tazobactam, clavulanate/ticarcillin).

[7]Polymyxins (colistin, polymyxin B).

[8]Tetracyclines (tetracycline, minocycline, doxycycline).

Table 4: Independent predictors of mortality among hospitalized patients with *Acinetobacter baumannii* infection

Predictor	**Adjusted odds ratio**	**Lower 95% confidence limit**	**Upper 95% confidence limit**
Current conditions			
Acute respiratory failure	3.94	3.07	5.05
Shock	3.05	2.36	3.94
Acute renal failure	2.01	1.62	2.49
Septicemia	1.62	1.27	2.08
Anemia	1.33	1.08	1.65
Inadequate initial treatment[1]	1.30	1.04	1.64
Infectious source			
Blood source	1.94	1.40	2.69
Respiratory source	1.64	1.29	2.09
Multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection[2]	1.66	1.30	2.12
Medical history			
Liver disease	2.15	1.46	3.17
Cancer or malignancy	1.40	1.11	1.76
Age, years	1.04	1.03	1.05

The adjusted odds ratios are estimated from multivariable analysis of the data. The final multivariable unconditional logistic regression model included all predictive variables listed in the table above (odds ratio >1) and controlled for the following variables: treatment with tigecycline, tetracyclines, polymyxins, fluroquinolones, and/or carbapenems, time to culture from admission,

osteomyelitis and infective arthritis, bacterial infection of an unspecified site, and year of treatment.

[1]Inadequate initial treatment was assessed from culture collection of the *A. baumannii* isolate until the 4th day after culture and defined as lack of receipt of at least one antibiotic with susceptibility.

[2]Multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection was defined as infection due to a MDR *A. baumannii* strain as compared to infection due to a non-MDR *A. baumannii* strain, either due to susceptibility or absence of susceptibility testing.

Table 5: Clinical outcomes among hospitalized patients with *Acinetobacter baumannii* infection overall and stratified by resistance

Clinical outcomes	All hospitalized patients with an *A. baumannii* infection (N = 4,599)	MDRAB infection* (N = 1,762)	Non-MDRAB infection (N = 2,802)	Adjusted odds ratio, (95% Confidence Interval)	CRAB infection** (N = 1,155)	Non-CRAB infection (N = 2,482)	Adjusted odds ratio, (95% Confidence Interval)
Inpatient mortality	626 (13.6%)	**409 (23.1%)**	**216 (7.7%)**	**1.61 (1.26-2.06)[a]**	**285 (24.7%)**	**210 (8.5%)**	**1.68 (1.31-2.17)[b]**
Mortality within 30 days of culture	676 (14.7%)	**391 (22.2%)**	**282 (10.1%)**	**1.71 (1.40-2.10)[c]**	**270 (23.4%)**	**266 (10.7%)**	**1.62 (1.29-2.04)[d]**
Reinfection within 30 days of discharge[1]	157/3,973 (4.0%)	**100/1,353 (7.4%)**	**55/2,586 (2.1%)**	**2.66 (1.88-3.77)[e]**	**68/870 (7.8%)**	**61/2,272 (2.7%)**	**2.31 (1.61-3.33)[f]**
Length of hospital stay greater than 10 days	2,411 (52.4%)	**1,210 (68.7%)**	**1,192 (42.5%)**	**1.25 (1.03-1.52)[g]**	**821 (71.1%)**	**1,112 (44.8%)**	**1.31 (1.04-1.65)[h]**
Readmission within 30 days of discharge[1]	935/3,973 (23.5%)	**341/1,353 (25.2%)**	**582/2,586 (22.5%)**	1.02 (0.87 - 1.19)[i]	215/870 (24.7%)	528/2,272 (23.2%)	0.95 (0.78 1.14)[j]

Data are n (%) or adjusted odds ratio (95% confidence interval).

Categorical variables were compared using chi-square or Fisher's exact tests where appropriate, means were compared using t-tests, and medians were compared using non-parametric Wilcoxon tests. Bolded indicates p-value <0.05 for comparison of resistant and non-resistant phenotypes.

The adjusted odds ratios are estimated from multivariable analysis of the data.

[1]Only measured among patients who were discharged alive.

*Multidrug-resistant *Acinetobacter baumannii* (MDRAB) infection was defined as *A. baumannii* infection due to an isolate that demonstrated non-susceptibility (intermediate or resistant) to at least 1 drug in at least 3 antibiotic classes (extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, and ampicillin/sulbactam). Non-MDRAB infection was defined as infection due to an isolate that demonstrated susceptibility to at least 1 drug in at least 3 antibiotic classes. Data not available in 35 patients to define MDRAB or non-MDRAB, as two or fewer antibiotic classes were tested for susceptibility.

**Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection was defined as *A. baumannii* infection due to an isolate that demonstrated non-susceptibility to at least 1 carbapenem (imipenem, meropenem, or doripenem). Non-CRAB infection was defined as infection due to an isolate that demonstrated susceptibility to at least 1 carbapenem. Data not available in 962 patients to define CRAB or non-CRAB, as no carbapenems were tested for susceptibility.

[a]Adjusted for the following current conditions (acute renal failure, acute respiratory failure, anemia, osteomyelitis and infective arthritis, septicemia, shock), medical history (cancer or malignancy, liver disease), infectious source (blood, respiratory), age, inadequate initial treatment, antibiotic treatment (carbapenems, fluoroquinolones, polymyxins, tigecycline), time to culture from admission, and year of treatment.

[b]Adjusted for the following current conditions (acute renal failure, acute respiratory failure, anemia, bacterial infection unspecified site, complication of surgical or medical procedure, septicemia, shock), medical history (cancer or malignancy, liver disease), infectious source (blood, respiratory), age, antibiotic treatment (carbapenems, fluoroquinolones, polymyxins, tetracyclines, tigecycline), time to culture from admission, and year of treatment.

[c]Adjusted for the following current conditions (acute renal failure, acute respiratory failure, anemia, bacterial infection unspecified site, fever, pneumonia, osteomyelitis and infective arthritis, septicemia, shock), medical history (cancer or malignancy, chronic obstructive pulmonary disease, liver disease), infectious source (blood, respiratory), age, antibiotic treatment (carbapenems, tigecycline) and year of treatment.

[d]Adjusted for the following current conditions (anemia, acute renal failure, acute respiratory failure, fever, osteomyelitis and infective arthritis, septicemia, shock, wound), medical history (cancer or malignancy, liver disease), infectious source (blood, respiratory), age, Charlson score, antibiotic treatment (carbapenems, polymyxins, tigecycline), and year of treatment.

[e]Adjusted for the following current conditions (acute respiratory failure), infectious source (blood), antibiotics in the prior 30 days, and year of treatment.

[f]Adjusted for the following current conditions (acute respiratory failure), infectious source (blood), antibiotics in the prior 30 days, nursing home stay in the prior 30 days, and year of treatment.

[g]Adjusted for the following current conditions (anemia, acute renal failure, acute respiratory failure, complication of device, implant, or graft, pneumonia, osteomyelitis and infective arthritis, septicemia), medical history (cancer or malignancy), infectious source (respiratory), age, inadequate initial treatment, antibiotic treatment (doxycycline, fluoroquinolones, piperacillin/tazobactam, polymyxins), intensive care unit treatment specialty, time to culture from admission, and year of treatment.

[h]Adjusted for the following current conditions (anemia, acute renal failure, acute respiratory failure, fever, complication of device, implant, or graft, pneumonia, osteomyelitis and infective arthritis, septicemia, wound), Charlson score, infectious source (respiratory), age, inadequate initial treatment, antibiotic treatment (doxycycline, fluoroquinolones, piperacillin/tazobactam, polymyxins), time to culture from admission, and year of treatment.

[i]Adjusted for the following current conditions (anemia), Charlson score, Elixhauser score, antibiotics in the prior 30 days, time to culture from admission, and year of treatment.

[j]Adjusted for the following current conditions (anemia, septicemia), Charlson score, antibiotics in the prior 30 days, and year of treatment.