

2022

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

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1

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4 patients with *Acinetobacter baumannii* infection

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6 **Running title:**

7 *Acinetobacter baumannii* infection mortality predictors

8

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26

27 **Word Count:** 2,471

28

29 **Author Contributions:**

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

31 Data generation: HA, ARC, VL

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

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

34

35 **Potential conflicts of interest disclosure:**

36 Haley Appaneal has received research funding from Shinogi.

37 Kerry LaPlante has received research funding or acted as a scientific advisor for Merck, Parateck,

38 Pfizer, Spero, and Shinogi.

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

41 No other financial disclosures.

42

43 **Funding:**

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

45

46 **Acknowledgements:**

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

50

51 **Compliance with ethics guidelines:**

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

56

57 **Consent for publication:**

58 Not applicable

59

60 **Data availability:**

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

64

65 **ABSTRACT:**

66 **WORD COUNT: 246**

67

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

70 **Methods:** Retrospective cohort study of inpatients with *A. baumannii* cultures and treatment from
71 2010-2019. Patients who died during admission were compared to those who survived to identify
72 predictors of inpatient mortality, using multivariable unconditional logistic regression models.

73 **Results:** We identified 4,599 inpatients with *A. baumannii* infection; 13.6% died during admission.
74 Fluoroquinolones (26.8%), piperacillin/tazobactam (24%) and carbapenems (15.6%) were used
75 for treatment. Tigecycline (3%) and polymyxins (3.7%) were not used often. Predictors of inpatient
76 mortality included current acute respiratory failure (adjusted odds ratio [aOR] 3.94), shock (aOR
77 3.05), and acute renal failure (aOR 2.01); blood (aOR 1.94) and respiratory (aOR 1.64) infectious
78 source; multidrug-resistant *A. baumannii* (MDRAB) infection (aOR 1.66); liver disease (aOR 2.15);
79 and inadequate initial treatment (aOR 1.30). Inpatient mortality was higher in those with MDRAB
80 vs. non-MDRAB (aOR 1.61) and in those with CRAB vs. non-CRAB infection (aOR 1.68). Length
81 of stay >10 days was higher among those with MDRAB vs. non-MDRAB (aOR 1.25) and in those
82 with CRAB vs. non-CRAB infection (aOR 1.31).

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

88

89 **WORD COUNT: 2,840; reference count 25**

90

91 **INTRODUCTION**

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

103

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

114

115 **METHODS**

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

118

119 The retrospective cohort study selected a cohort of adult inpatients (age \geq 18 years) admitted to
120 VA hospitals nationally with positive *A. baumannii* cultures from any infectious source (blood,
121 urine, respiratory, skin and tissue, and other) collected between January 1, 2010 and April 30,
122 2019. Further inclusion criteria consisted of antibiotic treatment with activity against *A. baumannii*
123 within 2 days of culture collection, treatment duration of 2 days or more, index culture and
124 susceptibility report completion time ten days or less, and the first qualifying admission meeting
125 these criteria during the study period. In the case of multiple positive *A. baumannii* cultures during
126 the admission, the first culture was considered the index culture.

127

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

138

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

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

149

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

154

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

166 > 1.0). Absence of collinearity between the variables in the final model was assessed from
167 tolerance and variance inflation.(9)

168

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

177

178 **RESULTS**

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

188

189 Current acute conditions and medical history are shown in Table 2. Those who died during
190 admission were significantly more likely to have current acute respiratory failure (75.7% vs.
191 23.6%), shock (44.2% vs. 7.6%), and acute renal failure (60.1% vs. 29.2%) than those who

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

196

197 Antibiotic treatment exposures for the study cohort are shown in Table 3. Fluoroquinolones
198 (26.8%) and piperacillin/tazobactam (24%) were the most used antibiotics. Carbapenems were
199 used in 15.6% of patients. Most carbapenem usage was as monotherapy (74.0%, n=530/716), as
200 was fluoroquinolone (63.6%, 783/1,232) and piperacillin/tazobactam usage (77.0%, n=849/1,102).
201 Combination therapy was used in 18.4% of patients. Only 3% of patients were treated with
202 tigecycline (53.3%, n=73/137 as combination therapy) and 3.7% with a polymyxin (55.0%,
203 n=93/169 as combination therapy). Those who died during were significantly more likely to be
204 treated with tigecycline (7.2% vs. 2.3%), a carbapenem (32.9% vs. 12.8%), or a polymyxin (12.9%
205 vs. 2.2%) than those who survived. Inadequate initial treatment was significantly more common
206 in those who died as compared to those who survived (59.9% vs. 46.5%).

207

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

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

219
220 Clinical outcomes can be found in Table 5. Most clinical outcomes were significantly worse for
221 those with MDRAB or CRAB infection, including inpatient mortality (MDRAB 23.1% vs. non-
222 MDRAB 7.7%; CRAB 24.7% vs. non-CRAB 8.5%) and length of stay greater than 10 days
223 (MDRAB 68.7% vs. non-MDRAB 42.5%; CRAB 71.7% vs. non-CRAB 44.8%). Inpatient mortality
224 was significantly higher in those with MDRAB vs. non-MDRAB (aOR 1.61; 95% CI 1.26-2.06) and
225 in those with CRAB vs. non-CRAB infection (aOR 1.68; 95% CI 1.31-2.17), and the odds of a
226 longer length of stay (>10 days) was significantly higher among those with MDRAB vs. non-
227 MDRAB (aOR 1.25; 95% CI 1.03-1.52) and in those with CRAB vs. non-CRAB infection (aOR
228 1.31; 95% CI 1.04-1.65). Results of subgroup analyses were generally similar to the overall cohort
229 (Table S2). However, the odds of a longer length of stay (>10 days) was significantly lower among
230 those with MDRAB vs. non-MDRAB (aOR 0.37; 95% CI 0.19-0.73) and among those with CRAB
231 vs. non-CRAB infection (aOR 0.37; 95% CI 0.16-0.86) in the subgroup of patients with blood
232 source infections and not significantly different for MDRAB or CRAB infections in the subgroup of
233 patients with respiratory source infections.

234

235 **DISCUSSION**

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

240

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

243 identified several predictors of mortality related to the severity of infection, including septicemia,
244 shock, acute respiratory failure, and acute renal failure.(7, 12) These conditions are all signs of
245 severe infection and resultant multiple organ dysfunction that are often present in critically ill
246 patients and contribute to poor outcomes including mortality.(12) We also identified that current
247 anemia was an independent predictor of mortality, in contrast to previous findings.(10) As patients
248 with anemia have low hemoglobin levels and may have disrupted transportation of oxygen to
249 organ systems leading to hypoxia, anemia may exacerbate multiple organ dysfunction seen in
250 critically ill patients thus contributing to excess mortality.(13) Additionally, in a previous study of
251 175 hospitals in the United States, anemia was more common among patients with MDRAB vs
252 non-MDRAB pneumonia and sepsis (50.6% vs. 38.5%, $p<0.001$); and hospital mortality was
253 higher in those with MDRAB.(14) Finally, our results may be related to the need for red blood cell
254 transfusion in patients with severe anemia. Previous work demonstrated that red blood cell
255 transfusion was a strong independent predictor of in-hospital mortality among patients with
256 MDRAB ventilator associated pneumonia.(15)

257
258 We also found that that underlying medical conditions (liver disease and cancer) and increasing
259 age were predictors of mortality, which is consistent with previous findings.(12, 16-18) Previously,
260 among two separate cohorts of hospitalized patients with *A. baumannii* bacteremia (n=188 and
261 n=122), malignancy was predictive of mortality.(18, 19) A meta-analysis of 19 observational
262 studies found that liver disease was an important factor associated with mortality in patients
263 infected with CRAB.(12)

264
265 Blood source and respiratory sources of infection were also predictive of mortality in our cohort.
266 These results are expected as pneumonia and bacteremia are generally associated with more
267 serious *A. baumannii* disease and worse patient outcomes than other infection types.(1)
268 Previous work among hospitalized patients with *A. baumannii* also demonstrated that blood

269 source of *A. baumannii* infection was an independent predictor of mortality (OR, 4.64, 95% CI,
270 1.26–17.06).(10) Bacteremia is an important and common cause of death. Previous work has
271 demonstrated that among patients with ventilator associated pneumonia (VAP) *A. baumannii*, the
272 mortality rate was higher in patients with VAP and bacteremia as compared to those with
273 nonbacteremic VAP (32.4% vs 9.6%, $P < 0.005$). (20) Pneumonia is also an important cause of
274 death. Previously, recovery of *A. baumannii* from the respiratory tract was identified as major risk
275 factor related to mortality among patients in the ICU with nosocomial *A. baumannii* infections. (21)
276 Among 338 patients with nosocomial *A. baumannii* bacteremia, bacteremia occurring after severe
277 pneumonia was an independent risk factor mortality. (16)

278
279 As with several previous studies, we found that MDRAB infection was an independent risk factor
280 for mortality. Infection with MDRAB often leads to high treatment failure and worse outcomes than
281 susceptible *A. baumannii* infection. A previous retrospective, matched cohort study in 2 hospitals
282 found that after controlling for severity of illness and underlying disease, MDRAB was
283 independently associated with increased hospital and intensive care unit length of stay as
284 compared to susceptible MDRAB. (3) The association between MDRAB infection and worse
285 clinical outcomes is likely related to increased probability for inappropriate initial antibiotic therapy,
286 delay to active antibiotics, and resultant increased severity of disease and increased risk for
287 treatment failure, rather than enhanced virulence of the organism. (17, 22-24) When controlling
288 for treatment and severity, MDRAB was still an independent predictor of mortality in our study. In
289 prior work, those with MDRAB were fivefold more likely to receive inappropriate empiric treatment
290 than those with non-MDRAB pneumonia or sepsis, and inappropriate empiric treatment nearly
291 doubled in-hospital mortality. (14)

292
293 As expected, clinical outcomes were significantly worse among those with MDRAB and CRAB as
294 compared to susceptible *A. baumannii* infections. Similarly, previous work has demonstrated that

295 resistant *A. baumannii* infections are associated with higher mortality and morbidity, including
296 increased length of hospital stay, readmission rates, and reinfection rates.(3) All-cause
297 readmissions and readmissions during which MDR organisms are isolated are common among
298 patients with infections due to MDR pathogens.(25) As with MDRAB, poor outcomes among those
299 with CRAB are likely related to inappropriate initial antibiotic therapy. A systematic review of
300 observational studies that included over 2,500 patient with CRAB and susceptible *A. baumannii*
301 infection found that CRAB was associated with a greater risk of mortality (OR 2.22, 95% CI 1.66-
302 2.98) and those with CRAB were more likely to receive inappropriate initial antibiotic therapy.(4)
303

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

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

323

324 In our national cohort of hospitalized patients with *A. baumannii* infection, 13.6% of patients died
325 during admission and clinical outcomes were worse for those with MDRAB or CRAB infection.

326 While most of the predictors we identified have been previously identified (separately or together

327 with other identified predictors) in various other studies of patients with *A. baumannii* infection,

328 mostly bacteremia and pneumonia, these studies did not control for differences in antibiotic

329 treatments. Additionally, our study is the first to identify this full list of predictors of inpatient

330 morality among hospitalized patients with all types of *A. baumannii* infection and the first to identify

331 anemia as an independent predictor. Controlling for antibiotic treatment, the predictors of inpatient

332 morality we identified included current conditions, infectious source, underlying illness, and

333 MDRAB infection. Our study may assist health care providers in the early identification of admitted

334 patients with *A. baumannii* infection who are at higher risk of death.

335

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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 <i>A. baumannii</i> 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 <i>Acinetobacter baumannii</i> (MDRAB) infection ¹	1,762 (38.3)	409 (65.3)	1,353 (34.1)	<0.001
Carbapenem-resistant <i>Acinetobacter baumannii</i> (CRAB) infection ²	1,155 (25.1)	285 (45.5)	870 (21.9)	<0.001
Resistance phenotype of index <i>Acinetobacter baumannii</i> 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
<i>Citrobacter</i>	81 (1.8)	15 (2.4)	66 (1.7)	0.194
<i>Enterobacter</i>	246 (5.3)	23 (3.7)	223 (5.6)	0.045
<i>Enterococcus</i>	857 (18.6)	88 (14.1)	769 (19.4)	0.002
<i>Escherichia coli</i>	466 (10.1)	57 (9.1)	409 (10.3)	0.360
<i>Klebsiella</i>	455 (9.9)	79 (12.6)	376 (9.5)	0.014
<i>Morganella morganii</i>	68 (1.5)	8 (1.3)	60 (1.5)	0.655
<i>Proteus mirabilis</i>	340 (7.4)	47 (7.5)	293 (7.4)	0.906
<i>Pseudomonas aeruginosa</i>	554 (12)	87 (13.9)	467 (11.8)	0.126
<i>Serratia marcescens</i>	60 (1.3)	15 (2.4)	45 (1.1)	0.010
<i>Staphylococcus aureus</i>	959 (20.9)	109 (17.4)	850 (21.4)	0.023
<i>Streptococcus pneumoniae</i>	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.

¹Multidrug-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.

²Carbapenem-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.

³Aminoglycosides (amikacin, gentamicin, tobramycin).

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

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

⁶Fluoroquinolones (ciprofloxacin, levofloxacin).

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

⁸Co-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 <i>A. baumannii</i> 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 <i>A. baumannii</i> 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.

¹Inadequate 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.

²Aminoglycosides (amikacin, gentamicin, tobramycin).

³Carbapenems (imipenem, meropenem, doripenem).

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

⁵Fluoroquinolones (ciprofloxacin, levofloxacin).

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

⁷Polymyxins (colistin, polymyxin B).

⁸Tetracyclines (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 <i>Acinetobacter baumannii</i> (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, fluoroquinolones, and/or carbapenems, time to culture from admission,

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

¹Inadequate 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.

²Multidrug-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 <i>A. baumannii</i> 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.

¹Only 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.

^aAdjusted 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.

^bAdjusted 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.

^cAdjusted 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.

^dAdjusted 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.

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

^fAdjusted 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.

^gAdjusted 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.

^hAdjusted 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.

ⁱAdjusted 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.

^jAdjusted for the following current conditions (anemia, septicemia), Charlson score, antibiotics in the prior 30 days, and year of treatment.