Published in final edited form as:

Am J Infect Control. 2010 February ; 38(1): 63–65. doi:10.1016/j.ajic.2009.05.007.

Antibiotic resistance determinants in *Acinetobacter spp.* and clinical outcomes in patients from a major military treatment facility

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Abstract

We explored the association of antibiotic-resistant phenotypes and genotypes in *Acinetobacter spp.* with clinical outcomes and characteristics in 75 patients from a major military treatment facility. Amikacin resistance was associated with nosocomial acquisition of *Acinetobacter baumannii*, and carbapenem resistance and *bla*_{OXA-23} were associated with the need for mechanical ventilation. The presence of *bla*_{OXA-23} also correlated with longer hospital and ICU stay. Associations between *bla*_{OXA-23} and complexity, duration, and changes made to antibiotic regimens also existed.

Multidrug-resistant (MDR) *Acinetobacter baumannii* is rapidly emerging as an important cause of nosocomial infection,^{1, 2} yet the clinical impact of isolating MDR *A. baumannii* in hospitalized patients is understudied.^{3,4,5,6} An outbreak of MDR *Acinetobacter spp.* across the US military health care system, associated with operations in Iraq and Afghanistan, has received widespread attention.⁷ A previous report focused on the antibiotic resistance genes responsible for the MDR phenotype in *Acinetobacter spp.* isolated from patients at the Walter Reed Army Medical Center (WRAMC).⁸ The present analysis examines whether different characteristics of *Acinetobacter spp.* such as antibiotic resistance genotype and phenotype, are associated with different clinical conditions and outcomes in that cohort of patients.

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Conflicts of interest: None to report. The opinions and assertions contained herein are the authors' alone and do not represent the views of the Walter Reed National Military Medical Center, the US Army, or the Department of Defense.

Methods

This is a cross-sectional study of the outcomes of 75 patients who were infected/colonized with *Acinetobacter* spp. while hospitalized at WRAMC between March 2003 and February 2005. Their medical records were examined retrospectively, with approval from the Institutional Review Board. Single patient isolates of *Acinetobacter* spp. were subjected to studies of antimicrobial susceptibility and detection of genetic determinants of resistance, as published previously.⁸ This collection included 1 *Acinetobacter* genome species 3, 1 *Acinetobacter johnsonii*, and 73 *A. baumannii* isolates.

Statistical analyses were performed to explore the association of antibiotic-resistant phenotype and/or genetic determinants of resistance in *Acinetobacter* spp. with clinical characteristics and outcomes. Associations of clinical variables with carbapenem and amikacin resistance, as well as associations with the presence of *bla*_{OXA-23} and *bla*_{OXA-58} (carbapenemase genes) were tested. The following variables were included: duration of hospitalization, duration of intensive care unit (ICU) stay, number and duration of antibiotics, number of changes in the antibiotic regimen, surgical procedures, APACHE II and Injury Severity scores, nosocomial infection (>72 hours after arrival), and mechanical ventilation. The variables were defined in relation to the entire hospital stay. In instances in which the variable was quantitative, the Mann-Whitney U test was applied. The relationship and correlation between continuous variables was evaluated with Spearman rank-order coefficient. The Statistical Package for the Social Sciences version 13 (SPSS, Chicago, IL) was used to analyze the data.

Results

Resistance to 3 or more classes of antibiotics was found in 89% of the isolates, and resistance to carbapenems was found in 24%. In addition, the *bla*_{OXA-23} gene was detected in 11%, and the *bla*_{OXA-58} gene was found in 12% of isolates.⁸ Our analysis revealed important clinical associations. First, amikacin-resistant isolates were more likely linked to nosocomial acquisition ($P=.009$) (Table 1). Second, *A. baumannii* expressing carbapenem resistance were isolated later in the outbreak than those susceptible to carbapenems ($P=.005$). Additionally, there was a relationship between requiring mechanical ventilation and infection with carbapenem-resistant *A. baumannii* ($P=.020$); this was also observed with isolates containing *bla*_{OXA-23} ($P=.041$) but not those possessing *bla*_{OXA-58} ($P=.156$) (Table 2). Associations also existed between *bla*_{OXA-23} containing isolates and the number of antibiotics used ($P=.026$), duration of antibiotic use in days ($P=.010$), and number of changes made to the antibiotic regimen ($P=.005$). Last, infection with *A. baumannii* strains containing *bla*_{OXA-23} (but not *bla*_{OXA-58}) was associated with a longer stay in the hospital ($P=.036$) and ICU ($P=.040$) (Table 2). Associations among resistance phenotypes or genetic determinants and mortality, APACHE II and Injury Severity scores, and surgical procedures were not found (data not shown). As previously reported, these strains were not all clonally related.⁸

Discussion

Our study shows that there are important and relevant associations in *A. baumannii* between certain resistance mechanisms, phenotypes, clinical characteristics and outcomes among a cohort of patients hospitalized at WRAMC. Three important conclusions are drawn. Most directly, this analysis reveals that *A. baumannii* strains that displayed carbapenem resistance were found later in the course of the outbreak. Carbapenem-resistant strains of *A. baumannii* may have been transferred, along with patients, to WRAMC from other military hospitals.⁸ Alternatively, this may reflect the increased use of this class of antibiotics for the treatment of infections and the resulting selection of carbapenem-resistant strains. In contrast, the isolation of amikacin-resistant isolates appeared to be more frequently associated with nosocomial acquisition of *Acinetobacter* spp. during hospitalization at WRAMC.

Secondly, isolates displaying carbapenem resistance were more frequently associated with patients requiring mechanical ventilation, but this association was only significant when carbapenem resistance was mediated by *bla*_{OXA-23}. This analysis, however, does not permit us to conclude whether carbapenem resistance resulted in more severe respiratory infection requiring mechanical ventilation or whether mechanical ventilation signifies a higher risk of acquiring carbapenemase-producing *A. baumannii*.

Most importantly, the OXA-23 carbapenemase, along with OXA-40 and OXA-58, are among the most common determinants of carbapenem resistance in *A. baumannii*.⁹ Our work suggests that infections caused by *A. baumannii* that harbor *bla*_{OXA-23} may be associated with more difficult to treat clinical conditions. This finding is supported by associations with 3 variables: number of antibiotics used, duration of antibiotic use, and number of changes in the antibiotic regimen. The presence of *bla*_{OXA-23} may signal a highly MDR phenotype, thereby increasing the complexity of antibiotic treatment and the need for changes to the antibiotic regimen. It remains to be shown as to whether the presence of *bla*_{OXA-23} translates into worse clinical outcomes. Although inferences regarding causality among the reported associations are not possible, our results suggesting an association between *A. baumannii* isolates harboring *bla*_{OXA-23} and longer hospital and ICU stays are especially noteworthy. Increased length of stay has been the most widely reported adverse clinical outcome in patients with *A. baumannii*, and it directly ties to the economic impact of these MDR organisms.^{3,4,5,6}

There are important limitations to consider in this analysis. We did not control for confounding factors such as severity of illness and underlying comorbidities nor did we assess the effect of appropriate or inappropriate antimicrobial therapy. It is also difficult at times for clinicians to distinguish colonization from infection, although perhaps colonization alone with certain *A. baumannii* strains may be a predictor of outcome.

Despite the limitations of this study, we believe that the associations between antibiotic resistance in *A. baumannii*, especially mediated by *bla*_{OXA-23}, and clinical outcomes deserve further consideration. Such information could guide and focus screening and infection control efforts. Our findings underscore the need for the continued examination of resistance determinants and clinical outcomes in this rapidly emerging pathogen.

Acknowledgments

Supported by the Veterans Affairs Merit Review Program, VISN 10 Geriatric Research Education and Clinical Center, and the National Institutes of Health (RO1 AI072219; to R.A.B.); by a fellowship sponsored by Wyeth Pharmaceuticals (to F.P.); and by the Veterans Affairs Merit Review Program (to C.J.D.).

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Table 1

Phenotypes and Outcomes.

Outcome	Carbapenem				Amikacin					
	R	S	P value		R	S	P value			
No. of isolates	19	56			40	35				
Intubation	17	34	.020*		26	25	.558			
No intubation	2	22			14	10				
HAI	5	19	.545		18	6	.009			
Non-HAI	14	37			22	29				
	Mean	SD	Mean	SD	P value	Mean	SD	P value		
No. days into outbreak	481.32	206.63	369.14	197.53	.005*	416.9	180.17	375.46	229.76	.802
No. of antibiotics	6.68	3.96	5.52	3.78	.182	6.08	3.53	5.51	4.19	.218
Duration of antibiotics, days	45.53	40.11	34.82	36.38	.395	38.2	31.57	36.77	43.55	.141
No. of antibiotic changes	6.68	4.41	4.7	4.54	.068	5.45	4.77	4.91	4.37	.597
Days ICU stay	20.21	34.88	18.52	35.01	.321	19.75	30.71	18.03	39.3	.463
Days inpatient	66.68	64.51	47.73	40.19	.535	54.68	42.11	50.09	54.04	.171

R, resistant; S, susceptible; HAI, hospital-acquired infection.

* P < .05.

Table 2

Genotype and Outcome.

Outcome	blaOXA-23				blaOXA-58					
	Positive	Negative	P value		Positive	Negative	P value			
No. of isolates	8	67			9	66				
Intubation	8	43	.041*		8	43	.156			
No intubation	0	24			1	23				
HAI	3	21	.729		1	23	.156			
Non-HAI	5	46			8	43				
	Mean	SD	Mean	SD	P value	Mean	SD	P value		
No. days into outbreak	488.38	215.7	386.72	202.02	.056	469.22	233.66	387.79	200.14	.094
No. of antibiotics	8.13	3.18	5.54	3.83	.026*	5	4.5	5.92	3.76	.279
Duration of antibiotics, days	71.63	45.16	33.46	34.53	.010*	23.44	21.49	39.45	38.76	.13
No. of antibiotic changes	8.75	3.2	4.78	4.54	.005*	3.56	3.32	5.42	4.68	.265
Days ICU stay	35.88	50.21	16.93	32.37	.040*	7.67	7.12	20.48	36.72	.632
Days inpatient	90.13	62.54	48.04	44.18	.036*	36.44	42.42	54.73	48.33	.172

NOTE: Positive refers to a present gene. Negative refers to an absent gene.

HAI, hospital-acquired infection.

* P < .05.