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RESEARCH ARTICLE

Acinetobacter spp in Intensive Care Unit: Risk Factors Associated with Infection and Fatality

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Abstract:

Purpose: *Acinetobacter* was known as a saprophytic colonizer, yet it is considered an important etiologic agent which is isolated from hospital-acquired infections. In this study, we aimed to investigate fatality rates, factors for fatality of *Acinetobacter* infections and relationship between combination therapies and survival.

Patients and Methods: We evaluated patients with Acinetobacter infection in ICU for demographic and clinical characteristics, combination therapies and adverse effects of these therapeutic options, retrospectively.

Results: Ninety-one patients with proved Acinetobacter infection were included in this study. We found that the fatality rate of Acinetobacter infection in ICU was 56%. Advanced age was significantly related with fatality. We found that carbapenem resistance increased steadily during a 5 year period, fatality rates significantly decreased with combination therapies including aminoglycosides. There wasn't significant relation between colistin therapy and survival in patients with Acinetobacter infections.

Conclusion: Critically ill patients with advanced age should be assessed thoroughly for Acinetobacter infection and prior carbapenem use. The empirical antibiotic treatment started earlier based on such risk factors may decrease fatality. The antimicrobial combinations including aminoglycoside may be considered more in order to the local resistance data.

Key words: Acinetobacter, Intensive Care Units, Fatality, Treatment, Istanbul

Introduction

Acinetobacter species is considered as pathogens with low virulence. Immunocompetent individuals do not develop disease easily. They usually cause hospital-acquired infections. The risk of infection with *Acinetobacter* species has increased in ICUs especially in patients, who need mechanical ventilation, lost his/her skin integrity due to a trauma or burn, has immunosuppression, was implanted with central venous catheter, has recently undergone a surgical operation, used fluoroquinolone, 3. generation cephalosporin and carbapenem and has enteral nutrition regime.(1) Acinetobacter infections have become more frequent and more serious problems in the daily medical practice of the infection diseases physicians upon increasing older population, use of new and stronger antibiotics, increase and diversification of interventional operations, and development of ICUs.This importance may attributed to its pan-resistance to antibiotics, survival in many environmental surfaces, ability to cause epidemics in the unit and severe morbidity, fatality and economic costs.(2, 3)

Guidelines have been developed by ECDC (European Centre for Disease Prevention and Control) and CDC (Centers for Disease Control and Prevention) joint venture to determine the antibiotic resistance characteristics of Acinetobacter species.(4) There are identified risk factors for colonization and infection with resistant microorganisms in the intensive care units.(5-7) First therapy option in infections with sensitive *Acinetobacter strain* is a monotherapy with the broad-spectrum cephalosporins (ceftazidime or cefepime), beta-lactam/beta lactamase combinations containing sulbactam or carbapenems (meropenem, imipenem or doripenem). However, it has been reported that resistance developed with monotherapy.(8, 9) Therefore, a combined therapy with an anti-pseudomonal fluoroquinolone or an aminoglycoside can be administered. Administration of polymyxin E (colistin) and tigecycline may be considered as an alternative treatment of multidrug resistant Acinetobacter infections. (10)

In this study, we aimed at investigating the demographic, epidemiologic and survival data of the hospital-acquired infections caused by *Acinetobacter*species in the intensive care units of our hospital.

Patients and Methods

Istanbul Sisli Hamidiye Etfal Training and Research Hospital is a training and research hospital with 900 beds. There are 3 intensive care units with 20 beds in total at our hospital. This study included patients, who admitted to the intensive care units between January 2008 and June 2013 and stayed for at least 48 hours in ICU, and was found Acinetobacter spp. in the culture reports obtained microbiology laboratory. The demographic data of these patients and their intubation and mechanical ventilation need during admission to ICU, presence of central venous catheter, recent application of surgical intervention, trauma, malignity, APACHE II score during admission and antibiotic treatments were recorded retrospectively from the computer system of the hospital. Acinetobacter infection was assessed according to specific criteria (CDC). Tracheal aspirate and urine cultures were performed quantitatively and catheter tip cultures were performed semi-quantitatively. According to CDC criteria(11) 66 patients, who did not have *Acinetobacter* infection criteria (12/66) and whose records could not be obtained (54/66) were excluded from the study.

Regression of infection findings was determined as the primary outcome, while fatality associated with *Acinetobacter* infection was determined as the secondary outcome. Fatality associated with *Acinetobacter* infection was assessed as the fatality up to day30^{th} following Acinetobacter growth in the culture. Creatinine values and Modification of Diet in Renal Disease (MDRD) equation(12) as well as renal functions from the initiation date of antibiotic treatment due to *Acinetobacter* infection was assessed in all patients administered with colistin. RIFLE (Risk, Injury, Failure, Loss, End Stage Kidney Disease) criteria, which were proven to be suitable for assessing renal functions with use of colistin(13-15), was used for identifying renal failure.

The microorganisms were defined as carbapenem resistant if Acinetobacter spp with zone diameter ≤ 13 mm for both imipenem and meropenem were recorded. Furthermore, carbapenem resistance was also assessed by Etest® (BioMerieux, USA) according to MIC.Antibiotic susceptibility was determined by the disc diffusion method and MIC values according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).(16)
Local ethic committee approval was obtained at May 2013.

Statistical Methods

Computer software (STATA v.12, StataCorp, Texas, USA) was used for statistical assessments. Data were reported as mean ± SD. Student t test, matched t test, χ^2 test, Mann Whitney U and Wilcoxon tests were used to univariate analysis. In univariate analysis two-tailed *P* value smaller than or equal 0.05 was used statistical significance level. Dependent variables were assessed using multi-variable logistic regression analysis. Kaplan-Meier graphic was used for survival analysis.

Results

The medical records of 157 patients, who were admitted to the intensive care units between January 2008 and June 2013 and determined to have *Acinetobacter* infection were assessed retrospectively. Ninety-one patients were included in the

study. The fatality rate of a total of 887 patients admitted to the intensive care units during the study period was 70%. In 91 patients included in the study, all-cause fatality rate was found to be 65% (n=60), while the fatality rate attributed to the *Acinetobacter* infections validated with the culture after occurrence of the systemic infection results was found to be 56% (n=51).

The demographical and clinical data of the patients as well as the risk factors determined for *Acinetobacter* infection in the literature were summarized in Table I.

Table I Demographical and Clinical Data and Risk Factors in Critically İll Patients with Acinetobacter Infection

Demographical Data	
• Number of patients	91
• Age (Year)	59 ±18
• Gender (M/F)	42/39
Clinical Data	
• APACHE II	16±6
• Duration of Hospitalization (day)	74±59
• Mechanical Ventilation	86
• Orotracheal Intubation	46% (42)
• Tracheostomy	48% (44)
Risk Factors	
• Recent surgical intervention	80% (73)
○ Brain Surgery	51% (47)
○ Others	29% (26)
• Neurological disease	41% (37)
• Trauma	29%(26)
• Malignity	25% (23)
• Diabetes Mellitus	18% (16)
• Cardiovascular disease	40% (36)

Clinical diagnosis in order to Acinetobacter infection site, simultaneous Acinetobacter bacteremia and average death days of the patients and fatality rate attributed to Acinetobacter Infection are summarized in table II.

Table II Clinical diagnosis, blood culture positivity and average mortality days

Diagnosis	**Percentage (Total)**	**Simultaneous Bacteremia**	**Average Death Time**	**Fatality Rate**
VAP/NP	54% (49)	65% (32)	13±7	67%
Meningitis	11% (10)	70%(7)	10±5	30%
SV Catheter infection	10% (9)	78% (7)	12±2	22%
Primary Bloodstream Infection	10% (9)	100% (9)	18±9	N/A
Soft Tissue Infection	6% (5)	20% (1)	20±9	N/A
Intraabdominal Infection	6% (5)	20% (1)	21±8	N/A
Urinary System Infection	4% (4)	50% (2)	18±9	N/A

Acinetobacter baumannii- calcoaceticus grown in the blood cultures of 59 (65%) out of ninety one patients, which were taken during systemic infection attack. There was no other systemic infection focus accompanying 9 (15%) of fifty nine bacteremia attacks and it was determined to be primary bloodstream infection. Of fifty nine bacteremia attacks, 32 (54%) were accompanied with VAP/HAP and 7 (11%) were accompanied by CV catheter infections, which were other Acinetobacter infections.

Eighty-four (92%) of the isolated strains were resistant to carbapenem. While the resistance to carbapenem was 84% in 2008, it was found to be 100% in 2012 ($p<0.05$). In 84 patients isolated with Carbapenem-resistant *Acinetobacter baumannii- calcoaceticus,* the number of patients receiving carbapenem during the last 3 months was 51 (61%), which is significantly higher ($p=0.01$) than patients which had no carbapenem history or was received at least 3 months before admission . All-infection fatality caused by infections of carbapenem-resistant species of *Acinetobacter* was found to be significantly higher ($p<0.05$). We couldn't evaluate resistance trend to colistin, because it was not in the market before 2011. No resistant origin was found since 2011, when the resistance to colistin was started to be investigated routinely.

Fatality was found to be 13 ±7 days in the VAP/HAP cases associated with *Acinetobacter*. Fatality rate was found 67% in the VAP/HAP attacks. The association between recent surgical intervention and other chronic diseases and fatality was not found to be significant in a single-variable analysis. While no statistical significance was determined in the multi-variable analysis model, it was found that *Acinetobacter* VAP/HAP fatality was 3 times higher in patients with malignity ($p=0.07$). Advanced age was found to be most important factor attributed to fatality of Acinetobacter infections.

A total of 10 *Acinetobacter* meningitis cases were included in the study. All *Acinetobacter* meningitis cases were associated with the recent brain surgery intervention. Eight (80%) of the isolated strains were resistant to carbapenem. Two (20%) of the patients with meningitis had bacteremia. Four of the cases had undergone operation due to a mass in MSS. Others had undergone brain surgery due to cerebrovascular diseases. Fatality associated with *Acinetobacter* meningitis was found to be 30% ($n=3$) in the patients included in our study.

Seven (78%) of nine central venous (CV) catheter infection attacks had accompanying bacteremia. Fatality was assessed as 22% ($n=2$) in CV catheter infections.

Colistin was used in treatment of all 36 patients. Acute renal failure associated with use of colistin was determined in 16 (44%) patients. The loading dose and high dose colistin (450 mg) were administered to 8 of 36 patients. Upon administration of two different doses of colistin, the fatality rate was found to be 64% in case of administration of low dose without loading, while it was found to be 50% in case of administration loading dose followed by a higher-dose maintenance treatment. No significant difference was found between the administration of low dose without loading dose and the loading dose followed by high dose of colistin in terms of renal failure. Mean duration of use of colistin in the group which developed renal failure, was 15±9 days, while it was 6±2 days in the group which did not develop renal failure. Such difference was not found to be statistically significant.

When 59 patients with growth in blood culture were assessed, no significant relationship with fatality associated with *Acinetobacter* was found. Average duration of stay at the ICU was 81±51 days in patients with Acinetobacter growth in blood culture, while it was 51±39 days in patients without Acinetobacter growth in blood culture. This difference was found to be statistically significant ($p<0.05$).

In a multi-variable analysis conducted to assess all risk factors and the fatality attributed to *Acinetobacter,* the mean age was found to be 64±16 in the fatality group and 53±19 in the survival group (OR:1.06, 95 %CI: 1.02-1.10, p=0.002). The analysis results were summarized in table III.

Table III Assessment of Factors Associated with Fatality by Multi-Variable Analysis

	Odds Ratio	**95% Confidence Interval**	**p**
Age	1.06	1.02 - 1.10	0.002
APACHE2	0.98	0.90-1.08	0.8
Trauma	0.38	0.13 - 1.12	0.08
Chronic Kidney Disease	4.61	0.74 - 28	0.10

The combined antibiotic treatments used during the study period are given in table IV.

Table IV Antibiotic combinations used in treatment

	n	**VAP**	**Other than VAP**
CP + CSB	9	4	5
CP+AG	12	6	6
AG+CSB	9	4	5
COL+TGC	12	6	6
COL+CP	12	3	9
COL+CSB	10	6	4
TGC+AG	10	7	3
CP+TGC	10	7	3

CP: Carbapenems CSB: Cefoperazone-Sulbactam AG: Aminoglicoside COL: Colistin TGC: Tigecycline

The relationship between the combined treatments used in all types of carbapenem resistant *Acinetobacter* infections and the survival rate was compared using regression analysis. It was found that the treatment, which was significantly effective on survival, was a combination of Cefoperazone-Sulbactam and one aminoglycoside (netilmicin in 20 patients and amikacin in 19 patients) (p=0.03). Whether each drug was studied alone, it was found that use of aminoglycoside was positively effective on survival (Fig 1). There was no difference between use of amikacin and netilmicin and survival.

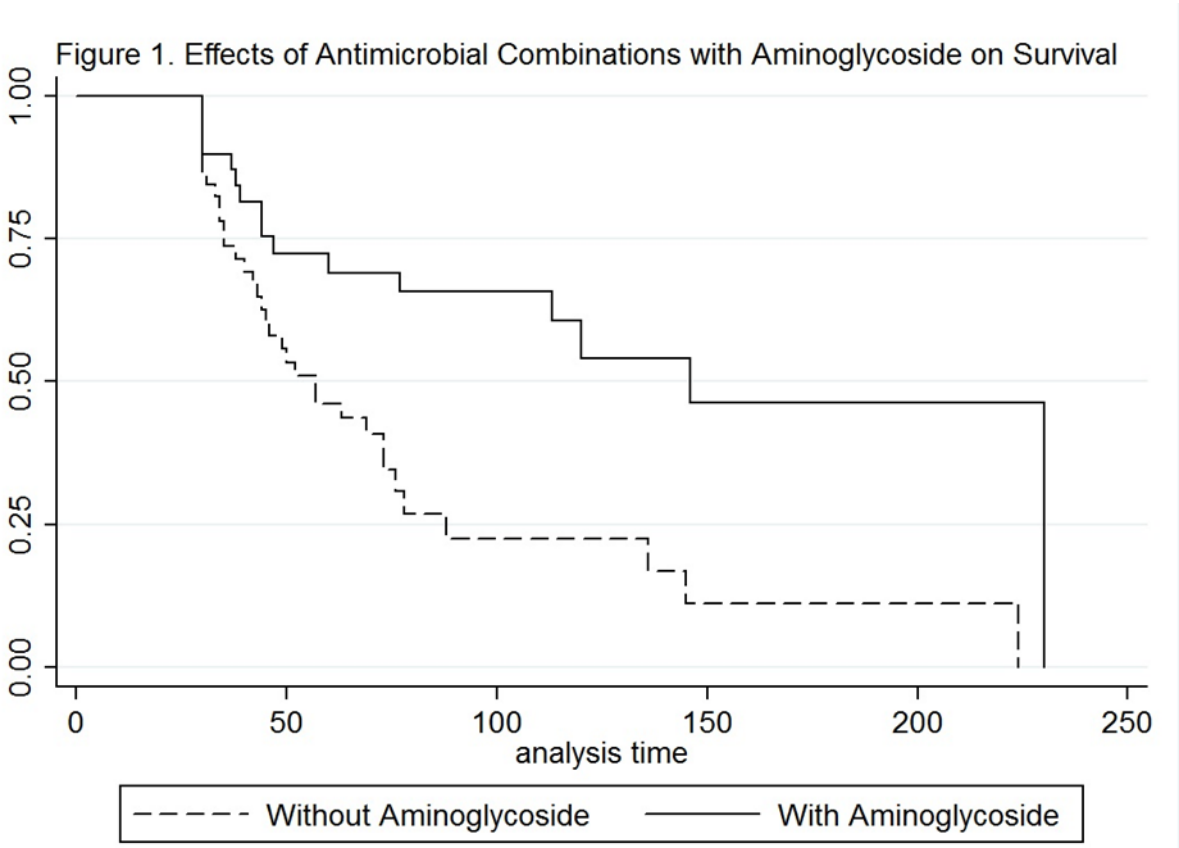

Figure 1. Effects of Antimicrobial Combinations with Aminoglycoside on Survival

Discussion

Acinetobacter species may cause suppurative infections on each organ and system.(17) Among *Acinetobacter* species, the most important one that is responsible for infections at ICUs is *A. baumannii.* The most commonly observed pathology is ventilator associated pneumonia and primary bloodstream infection. According to a report published by USA National Health Services Security Network (NHSN) in 2008, of *Acinetobacter* isolates, 8.4% is responsible for VAP, 2.2% is responsible for primary bloodstream infection, 1.2% is responsible for urinary system infection associated with catheter and 0.6% is responsible for infection at surgical area.(18) The crude mortality rate of *Acinetobacter* infections varies between 26% and 68%.(19) In a review published by Falagas et al in 2006, it was reported that the fatality rates attributed to Acinetobacter infections in the intensive care units ranged between 10% and 43%.(20)

Acinetobacter spp. currently appears as a causative agent of hospital-acquired infection - especially in ICUs - and causes the most common hospital-acquired pneumonia. Most of the hospital-acquired pneumonia are observed in the patient group, who receive mechanical ventilation.(21) In our study respiratory system involvement was most frequent Acinetobacter infection. This finding is in compliance with the literature data. According to our findings, the second most common infection type was meningitis. In many publications, it was reported that the meningitis cases caused by *Acinetobacter* species were observed less

commonly.(22) This may be explained by frequent intracranial mass and arteriovenous malformation operations performed in our hospital and the fact such patients stay together with the other intensive care patients, when they require intensive care. The rate of meningitis associated with *Acinetobacter* species can be decreased by checking the information and compliance of the personnel about application and maintenance of catheters and their compliance to the infection control measures.

The fatality rate attributed to the hospital-acquired infections caused by *Acinetobacter* species varies between 7% and 43%.(20, 23) Such data vary based on the characteristics of the clinic, where the patient stays, or place of involvement. Severe disease, old age, inappropriate antimicrobial treatment, bacteremia associated with pneumonia, increased serum creatinine, presence of malignity, mechanical ventilation and resistance to carbapenem.(24) Such risk factors for fatality were assessed in our study. The all-cause fatality rate in the patients admitted to the intensive care unit during the study period was found to be 70% and, when 91 *Acinetobacter* infection attacks during this period were considered, the fatality rate attributed to *Acinetobacter* infections was found to be 56%. The independent risk factor statistically significant with the fatality included old age. In addition, isolation of *Acinetobacter* species from respiratory secretions was determined to be a factor increasing the fatality significantly. APACHE2 mean of the included patients was found to be 16±5. We cannot find correlation between APACHE 2 score and fatality.

The recommended dose of colistin, which has been widely available during the last 6 months of 2010 in Turkey, was 2.5-5 mg/kg (mean 300 mg/day) according to the guidelines. From 2012, administration of the loading dose (300 mg) and higher dose in maintenance (450 mg/day)(25, 26) has become more common. In a meta-analysis, it was shown that intravenous colistin did not cause more nephrotoxicity compared to the other antibiotics.(10, 27) And in our hospital, the doses administered until the first 6 months of 2012 was 2.5-5 mg/kg (n=28) followed by the loading dose and higher doses in maintenance (n=8) according to the guidelines. Colistin was administered in combination with cefoperazone-sulbactam, carbapenem (imipenem or meropenem) or tigecycline. In case of carbapenem-resistant Acinetobacter infections, the combination treatments with colistin did not show a significant decrease in the fatality compared to the other treatments. An increase was observed in the acute renal failure upon administration of colistin, but it was not significant. No increase was observed in the acute renal failure upon administration of high dose of colistin. Further studies are required to assess the impact of the treatment on fatality and nephrotoxicity.

As alternative drug, aminoglycosides are recommended for carbapenem resistant Acinetobacter infections in combinations.(22) Use of aminoglycosides in the combination treatment (netilmicin or amikacin) in our study was found to be associated with low fatality in the patients infected with carbapenem resistant Acinetobacter infections. Nowadays, resistance to antibiotics has increased from day to day with decreasing number of treatment options, we can recommend more rational use of aminoglycosides in treatment methods in case of carbapenem resistant Acinetobacter infections. Further studies are required to validate this situation.

In conclusion, critically ill patients with advanced age should be assessed thoroughly for Acinetobacter infection and prior carbapenem use. The empirical antibiotic treatment started earlier based on such risk factors may decrease fatality. The antimicrobial combinations including aminoglycoside may be considered more in order to the local resistance data.

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