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Treatment Combinations and Prognosis in Multiple Resistant *Acinetobacter baumannii* and Carbapenem Resistant *Klebsiella pneumoniae/oxytoca* Isolates

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Abstract

Background: Multi-drug-resistant (MDR) gram-negative bacterial infections are one of the most important causes of prolonged hospitalization and mortality in patients followed up in the Intensive Care Unit (ICU). In my study, we retrospectively scanned the blood and tracheal aspirate cultures (TAC) of patients hospitalized in the ICUs of my hospital.

Materials and Methods: We investigated the effects of demographic characteristics, comorbid conditions, treatment combinations and time of treatment on survival of 83 patients with MDR *Acinetobacter baumannii* and *Klebsiella pneumoniae/oxytoca* strains in culture samples from 450 cases.

Results: Of the patients, 48 (57.83%) were male, and 35 (42.17%) were female. Of all cases, the average age (years) was average±SD (Min-Max), 76.24±13 (23-96). Length of stay in intensive care, the average (day) was 25.61±19.1 (1-107). Cerebrovascular Disease (CVD) was the most common (20%) comorbidity. *A. baumannii* was grown in 31 (37.3%) patients, *K. pneumoniae* was grown in 50 (60.3%) patients, and *K. oxytoca* was grown in 2 (2.4%) patients. Age (p=0.793), sex (p=0.429), length of hospital stay (p=0.097), number of comorbidities (p=0.553), treatment combinations (p=0.727), pathogen type (p=0.622), growth in blood culture and/or TAC (p=0.369), there was no statistically significant difference indicating that factors such as increased mortality. It was observed that intubation (p=0.004) and duration of treatment of 7 days or less (p=0.001) significantly reduced survival.

Conclusions: Pneumonia and bloodstream infections due to XDR or PDR *Acinetobacter* and CR *Klebsiella* are important problems in hospitalized patients due to the need for intensive care unit. Despite monotherapy or combination therapy with available antibiotics, mortality remains a serious problem. Protection of patients from intubation and adequate treatment duration are important factors affecting survival. New antibiotic studies are needed to diversify the treatment alternatives and to keep the increasing antibiotic resistance under control in XDR or PDR gram negative bacillus infections.

Key words: *Multiple resistance, carbapenem resistant, acinetobacter baumannii, klebsiella pneumoniae/oxytoca, colimycin, tigecycline.*

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Introduction

Treatment options are increasingly difficult to find, as the increase in MDR Gram-negative bacteria is faster than the discovery of new antibiotics (1). In the treatment of Carbapenem-Resistant Enterobacteriaceae (CRE) species and *Acinetobacter* infections, colistin, tigecycline, amikacin and fosfomycin and their combinations with each other or with carbapenems are used. It has been reported that combined treatment, especially with regimens containing carbapenem, is superior to monotherapy (2, 3, 4). Infections with MDR, common drug resistant (XDR) and pan-drug resistant (PDR) microorganisms are associated with increased rates of intensive care hospitalization, mortality and morbidity (4). Infection control measures are the most important factor in preventing the spread of this type of resistant infections, especially in ICU (5, 6).

The aim of this study was to investigate the treatment combinations and the effects of these combinations on prognosis in multiresistant *A. baumannii* and carbapenem resistant *K. pneumoniae/oxytoca* isolates in my hospital.

Materials and Methods

Clinical data collection

Blood culture and TAC samples taken from 450 patients aged 18 years and older who were followed up in the intensive care units of Ordu State Hospital between 1 May 2020 and 2 July 2021 were scanned retrospectively. 83 patients with *K. pneumoniae/oxytoca* and *A. baumannii* growth resistant to all antibiotics such as carbapenem, 3rd generation cephalosporin, quinolone, ampicillin sulbactam, piperacillin tazobactam were included in the study (Table 1). Age, sub-disease, intubation, mortality, length of hospital stay, reproducing pathogen, antibiotic resistance status, duration of treatment and treatment combinations (Carbapenem, Aminoglycoside, Colymycin, Tigecycline, Fosfomycine) of the patients were recorded. Cases with a history of COVID-19 diagnosis and those with carpanem-susceptible pathogen growth were excluded from the study.

Table 1. Isolates and antibiogram results.

Sample Information	**Tracheal Asp / B. Lavage Culture**		
Microorganism	***A. baumannii***	**Colony amount**	**100.000 cfu/ml**
Antibiogram	**Antibiotic name**	**Status**	**MIC**
	Gentamicin	Resistant	>8
	Imipenem/cilastatin	Resistant	>8
	Levofloxacin	Resistant	>4
	Meropenem	Resistant	>8
	Ciprofloxacin	Resistant	>1
	Tobramycin	Resistant	>8
	Amikacin	Resistant	>32
	Trimethoprim-sulfamethoxazole	Resistant	>8/152
Sample Information	**Blood Culture**		
Microorganism	***K. pneumoniae ssp pneumoniae***	**Colony amount**	**100.000 cfu/ml**
Antibiogram	**Antibiotic name**	**Status**	**MIC**
	Amoxicillin/Clavulanic Acid	Resistant	>16/2
	Ceftazidime	Resistant	>8
	Ceftriaxone	Resistant	>4
	Gentamicin	Resistant	>8
	Imipenem	Resistant	>8
	Levofloxacin	Resistant	>2
	Meropenem	Resistant	>8
	Ciprofloxacin	Resistant	>1
	Ampicillin	Resistant	>16
	Piperacilin/Tazobactam	Resistant	>16/4
	Cefuroxime	Resistant	>16
	Amikacin	Resistant	>32
	Trimethoprim/Sulfamethoxazole	Resistant	>8/152
	Sefepim	Resistant	>8
	Colistin	Resistant	>1

Bacterial Isolates Identification and Antimicrobial Susceptibility

Bacterial identification and antimicrobial susceptibility tests were conducted by the BD Phoenix Automated Microbiology System (USD). Since it would not be appropriate to analyze the sensitivity of Colimycin and Tigecycline with an automated system, the resistance status of these two antibiotics was not recorded in the reproducing pathogens.

Statistical Analysis

Ver 26.00 (SPPS Inc. Chicago, IL, USA) program was used. The p value of <0.05 was considered statistically significant. Independent sample Mann-Whitney U test was used for the analysis of data that did not show normal distribution. Categorical variables were compared with "Pearson Chi Square" or "Fisher's exact test".

Results

Prevalence of symptoms

A total of 83 patients were included in the study. Of the patients, 48 (57.83%) were male, and 35 (42.17%) were female. Of all cases, the average age (years) was average±SD (Min-Max), 76.24±13 (23-96). Length of stay in intensive care, the average (day) was 25.61±19.1 (1-107). CVD was the most common (20%) comorbidity, while there were other comorbidities of Heart Faılure (HF) (19%), Hypertensıon (HT) (18%), Diabetes Mellitus (DM) (14%), Chronıc Obstructıve Pulmonary Dısease (COPD) (11%) and malignancy

(TM) (9%). 89% of the patients were intubated. It was observed that 48 (57.83%) of the cases were mortal. There was growth in TAC of 48 (69.9%) patients, in blood cultures of 12 (14.5%) patients, and in both cultures of 13 (15.6%) patients. *A. baumannii* was grown in 31 (37.3%) patients, *K. pneumoniae* was grown in 50 (60.3%) patients, and *K. oxytoca* was grown in 2 (2.4%) patients. While *A. baumannii* was resistant to all antibiotics of fosfomycin, carbapenem, quinolone and aminoglycoside group, *K. pneumoniae/oxytoca* were 86% resistant to aminoglycosides, all carbapenems and quinolones (Table 2).

Table 2. Antibiotic resistance rates.

	Resistance n (%)	
Antibiotics	***A. baumannii***	***K. pneumoniae/oxytoca***
Fosfomycine	22(100)	48(98)
Carbapenem	31(100)	52(100)
Aminoglycoside	30(100)	45(87)
Ciprofloxacin	30(100)	52(100)
Levofloxacin	30(100)	52(100)

When the treatment combinations of the cases were examined, it was seen that Carbapenem+Colimycin was preferred most frequently in *A. baumannii* infections, and in *K. pneumoniae/oxytoca* infections. Those who received treatment other than Carbapenem, Aminoglycoside, Colimycin, Tigecycline, Fosfomycine group antibiotics or who did not receive any antibiotic treatment were also specified in the no treatment group (Table 3).

Table 3. Treatment combinations.

	***A.baumannii*n n(%)**	***K. pneumoniae/oxytoca* n (%)**
Treatment Combination		
Colymycin+Fosfomycin	0	2 (2.4)
Colymycin+ Aminoglycoside	0	1 (1.2)
Fosfomycin	0	1 (1.2)
Fosfomycin + Tigecycline	0	1 (1.2)
Carbapenem+Aminoglycoside	5 (6)	5 (6)
Carbapenem+Colymycin+ Fosfomycin	1(1.2)	7 (8.55)
Carbapenem+Colymycin[1]	12(14.5)	8 (9.6)
Carbapenem+Aminoglycoside+ Colymycin	1(1.2)	4 (4.8)
Carbapenem [2]	3(3.6)	7 (8.55)
Carbapenem+Colymycin+ Tigecycline	1 (1.2)	4 (4.8)
Carbapenem+Fosfomycin	0	3 (3.6)
Carbapenem + Tigecycline	3(3.6)	0
Carbapenem+Aminoglycoside+ Colymycin+Tigecycline	0	1 (1.2)
Aminoglycoside [3]	0	1 (1.2)
Carbapenem+Aminoglycoside+ Tigecycline	0	1 (1.2)
Carbapenem+Aminoglycoside+ Fosfomycin	0	1 (1.2)
No Treatment [4]	5(6)	5 (6)
Total n, (%)	**31 (37.3)**	**52 (62.7)**

(1): Carbapenem+colimycin was combined with trimethoprim sulfamethoxazole in one patient and ampicillin sulbactam in other patient. (2): A combination of carbapenem and quinolone was used in three patients. (3): In one patient, aminoglycoside was combined with tirmethoprim sulfamethoxazole. (4): Two patients had excitus shortly after hospitalization. 1 patient received Cefaperazon Sulbactam, 2 patients received Pieperacillin Tazobactam, 1 patient received Pieperacillin Tazobactam + Vancomycin. 4 patients did not receive any treatment.

Age (p=0.793), sex (p=0.429), length of hospital stay (p=0.097), number of comorbidities (p=0.553), treatment combinations (p=0.727), pathogen type (p=0.622), growth in blood culture and/or TAC (p=0.369), there was no statistically significant difference indicating that factors such as increased mortality. It was observed that intubation (p=0.004) and treatment duration of 7 days or less (p=0.001) significantly reduced survival (Table 4).

Table 4. Effect of demographic characteristics and treatment protocol on prognosis

Case	Death group	Survivor group	p value
Age, average±SD (Min-Max)	76.35±11.68(47-92)	76.09±14.87(23-96)	0,793
Sex			
Male	26(31.2)	22(26.6)	0,429
Female	22(26.6)	13(15.6)	
Hospitalization, average±SD (Min-Max)	23.29±18.89(1-81)	28.80±19.25(3-107)	0,097
İntubation			
Yes	47(56.6)	27(32.6)	**0,004**
No	1(1.2)	8(9.6)	
Comorbidity			
Single	25(30.1)	22(26.6)	0,553
Two	16(19.2)	8(9.6)	
Three or over	7(8.5)	5(6)	
Culture			
TAC	34(41)	24(28.9)	0,369
Blood	5(6)	7(8.5)	
TAC and Blood	9(10.8)	4(4.8)	
Isolate			
A. baumannii	19(22.9)	12(14.5)	
K. pneumoniae/oxytoca	29(34.9)	23(27.7)	0,622
Treatment Combination			
Single	8(9.6)	4(4.8)	
Dual	23(27.7)	17(20.5)	0,727
Triple or over	11(13.3)	10(12.1)	
No treatment	6(7.2)	4 (4.8)	-
Duration of treatment			
≤7 days	30(36.1)	9(10.9)	**0,001**
>7 days	18(21.7)	26(31.3)	
Total n(%)	**48(57.8)**	**35(42.2)**	**100 (100)**

Discussion

MDR or PDR *Acinetobacter* species and CRE species cause infections with limited treatment options and with serious mortality and morbidity (4,7-10). XDR gram-negative bacilli become resistant to all antimicrobials in general, not just to a single antibiotic group, with their resistance mechanisms (11, 19-21). The number of XDR gram-negative bacilli has increased in recent years (22). In a study conducted to determine the in vitro efficacy of tigecycline in *A. baumannii* and carbapenem resistant *K. pneumoniae* isolates that are

completely resistant to all antibiotics except MDR or colistin, the rate of meronepem resistance was found to be 59% for *A. baumannii* and 100% for *K. pneumoniae*. In addition, the rate of resistance to amikacin was reported as 70% and 52%, and the rate of resistance to ciprofloxacin was reported as 88% and 92.1%, respectively (12).

Similarly, in my study, it was observed that CR causative pathogens isolated from TAC and blood culture developed high rates of resistance to antibiotics such as quinolones, aminoglycosides and fosfosmycin, which are frequently preferred in monotherapy or combined treatment with carbapenem.

In a study evaluating 720 patients, CR *Klebsiella spp*. amoxicillin clavulanate, colistin, trimethoprim sulfamethoxazole, piperacillin tazobactam, ciprofloxacin, gentamicin, amikacin (100%, 100%, 88.1%, 80.9%, 73.8%, 71.4%), respectively. It has been reported as 59.5% (13). Tijet et al. İn a study evaluating the susceptibility of clinical carbapenemase-producing isolates, the most sensitive antibiotics were found to be tigecycline (100%), colistin (93%), and gentamicin (53.3%), respectively. Amikacin and tobramycin sensitivities were reported as 23.3% and 6.7% (14). It is emphasized that there is insufficient evidence-based data that combination therapies are better for many combination therapies, including colistin/carbapenem, which are used against CR gram-negative bacilli, and a clear recommendation cannot be reached in this regard (15, 16). On the other hand, in a study by Lee and Burgess comparing combination therapy and monotherapy, it was reported that treatment failure was significantly higher in patients receiving monotherapy (49%-5%, respectively; p=0.01). Combination treatments were compared among themselves, and it was reported that no significant difference was found between treatment groups (17). In another study in which 84 patients hospitalized in the burn unit were compared with colistin monotherapy and colistin-based combination treatments, no significant difference was observed between monotherapy and combination treatment in terms of 30-day mortality. But duration of antibiotics were associated with 30-day mortality (23). In another recent randomized controlled study, it was not shown that the combination of colimycin+meropenem was superior to colimycin monotherapy in CR gram-negative bacillus infections (24).

Similar to the studies performed in our study, aminoglycoside susceptibility to CR *K. pneumoniae* strains was found to be higher than that of fosfomycin and quinolone, creating an alternative in combination. The most common treatment for both strains detected in our center was the combination of carbapenem + colimycin. However, no significant superiority in survival of monotherapy or combination treatments was observed in both *A. baumannii* and CR *K. pneumoniae* (p=0.727). In our study, the duration of treatment stand out. Especially in treatments shorter than one week, the survival rate decreased significantly (p=0.001).

In an intensive care study in which 37 patients with MDR hospital-acquired *A.baumannii* infection and 181 patients without MDR A.baumannii infection were included, re-intubation and tracheotomy rates were found to be higher in patients infected with *A.baumannii* compared to the control group. While there was no significant difference between the groups in terms of mortality, the duration of ICU and hospital stay was longer in the MDR group (24.2 ± 18.3 vs. 8.2 ± 8.3 days, p< 0.001 and 33.3 ± 19.8 vs. 15.4 ± 11.4 days, p< 0.001) (16). In another similar study, two groups with MDR *Acinetobacter* and without MDR *Acinetobacter* were compared, and it was found that there was no significant

difference between the groups in terms of length of stay in intensive care unit and hospital stay (25).

In my study, when all cases were examined, hospitalization was found to be average±SD (Min-Max) in the death group and the living group (23.29±18.89(1-81) and 28.80±19.25(3-107)), respectively. No significant effect on survival was observed (p=0.097). However, the fact that patients did not need intubation significantly affected the survival rate (p=0.004).

Conclusion

Pneumonia and bloodstream infections due to XDR or PDR *Acinetobacter* and CR *Klebsiella* are important problems in hospitalized patients due to the need for intensive care unit. Despite monotherapy or combination therapy with available antibiotics, mortality remains a serious problem. Protection of patients from intubation and adequate treatment duration are important factors affecting survival. New antibiotic studies are needed to diversify the treatment alternatives and to keep the increasing antibiotic resistance under control in XDR or PDR gram negative bacillus infections.

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