DETECTION OF SYNERGISTIC ANTIMICROBIAL ACTIVITIES BETWEEN DORIPENEM, TIGECYCLINE AND COLISTIN AGAINST MULTI-DRUG-RESISTANT ACINETOBACTER BAUMANNII STRAINS OBTAINED FROM PATIENTS IN INTENSIVE CARE UNITS

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ABSTRACT

Introduction*: Acinetobacter baumannii (A. baumannii) is an opportunistic pathogen leading to nosocomial epidemics and multidrug-resistant (MDR) isolates are making the treatment of these infections more complicated. Combinations of antibiotics acting by different mechanisms are used for the treatment of MDR bacterial infections. In this study we evaluated the minimum inhibitory concentrations (MICs) of colistin (CO), doripenem (DOR), tigecycline (TIG) alone and in vitro synergistic activity of CO-DOR, CO-TIG and DOR-TIG combinations against MDR A. baumannii strains isolated from patients in intensive care units (ICUs).*

Materials and methods*: Thirty A. baumannii strains isolated from various clinical specimens of patients in ICUs were included in the study. The epsilometer test (E-test) method was used for determining the synergistic activity of different antibiotic combinations. Synergistic, additive, indifferent and antagonist effects of A. baumannii strains were evaluated by Fractional Inhibitory Concentration (FIC) index .*

Results*: Of the 30 MDR A. baumannii strains tested, 90% were susceptible to TIG, 93.3% to CO and 50% to DOR. CO-DOR, CO-TIG and DOR-TIG combinations were found to have synergistic or additive effects against 3 (9.9%), 5 (16.6%) and 4 strains (13.3%), respectively. The synergistic or additive effect of DOR-TIG combination was 19.9% for DOR resistant strains and 6.6% for DOR susceptible strains. The synergistic or additive effect of CO-DOR combination was 19.9% for DOR resistant strains and 0% for DOR susceptible strains.*

Conclusion*: Among the tested antimicrobial combinations, the combination of CO with TIG was most effective against MDR A. baumannii strains isolated from patients in ICUs. The synergistic or additive effects both for CO-DOR and DOR-TIG combinations were higher in DOR resistant strains. This study suggested that combination therapy with DOR for treating MDR A. baumannii infections should be used especially in DOR resistant strains.*

Keywords*: Acinetobacter baumannii, epsilometer test, synergy, intensive care unit.*

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Introduction

Acinetobacter baumannii (*A. baumannii*) is ubiquitous in nature and has been recovered from soil, water, animals and humans. Acinetobacter species are normal inhabitants of human skin and are frequently isolated from the throat and respiratory tract of hospitalized patients[(1)].

Multidrug-resistant (MDR) *A. baumannii* is a rapidly emerging pathogen in the health care settings, where it causes infections that include bacteremia, pneumonia, meningitis, urinary tract infection and wound infection. This organism usually affects immunocompromised, ventilator-dependent or debilitated patients. The organism's ability to survive under a wide range of environmental conditions

and to persist for extended periods of time on surfaces, make it a frequent cause of outbreaks of infection and an endemic, health care-associated pathogen[2,3].

A. baumannii has been observed as a serious nosocomial pathogen which causes high mortality rates (26-68%), increased hospitalization costs and prolonged length of hospital stays particularly common in intensive care units (ICUs)[4]. The EPIC (Extended Prevalence of Infection in Intensive Care) II study group revealed an international prospective point prevalence study. The data were collected from 13796 patients in 1265 participating ICUs from 75 countries. The *Acinetobacter* infection rates were 19.2% in Asia; 17.1% in Eastern Europe; 14.8% in Africa; 13.8% in Central and South America; 5.6% in Western Europe; 4.4% in Oceania and 3.7% in North America [5].

The first options in treatment of patients infected by *A. baumannii* strains are carbapenems if they are sensitive to them. However, significant treatment-related problems are experienced today due to the problem of increasing resistance of MDR *A. baumannii* strains to many groups of antibiotics including carbapenems. The empirical treatment started is often not appropriate due to the problem of resistance. For example, the rate of carbapenem resistance of MDR A. baumannii isolates in Turkey is more than 50%[6]. The high resistance rates of *A.baumannii* to commonly used antibiotics, including carbapenems, limit the therapeutic options and have necessitated the need for combination therapy. Although combination therapy is frequently used in clinical practice, more evidence is needed to support its use instead of monotherapy[7,8].

In this study we determined the minimum inhibitory concentration (MIC) values of colistin (CO), doripenem (DOR), tigecycline (TIG) alone and in vitro synergistic activity of CO-DOR, CO-TIG and DOR-TIG combinations by Epsilometer test (E-test) against MDR *A. baumannii* strains isolated from patients in ICUs.

Materials and methods

A total of 30 MDR *A. baumannii* strains isolated from patients in Etlik İhtisas Training and Research Hospital were evaluated. Ten (33.3%) isolates were obtained from blood, 9 (30%) from tracheal aspirate, 6 (20%) from wound, 3(10%) from urine and 2(6.6%) from catheter samples of the patients in surgical, internal and anesthesia ICUs.

The identification and susceptibility tests of *A. baumannii* strains were performed by using an automatized system (VITEK 2, bioMerieux, France). MDR *Acinetobacter baumannii* isolates were defined as resistant to more than three classes of antibiotics[9]. Antibiotic susceptibility tests and the MIC values were interpreted according to the standards of Clinical and Laboratory Standards Institute (CLSI)[10].

The MIC values and the synergy tests were determined by using the E-test method, according to the manufacturer's instructions (bioMerieux, France). The MIC values were assessed: first for CO, DOR and TIG alone, then in combination (CO-DOR, CO-TIG and DOR-TIG) for each of the MDR *A. baumannii* isolates. Bacterial suspensions, prepared to 0.5 MacFarland standard turbidity, were spread onto 150 mm Mueller-Hinton agar plates. Etest strips (bioMerieux, France) for CO, DOR and TIG were placed onto the inoculated plates. Then the plates were incubated for 24 h at 37°C and the MIC values were recorded.

Three different antibiotic combinations (CO-DOR, CO-TIG and DOR-TIG) were evaluated for in vitro synergistic effect by the E test method (bioMerieux, France). The E test strip of an antibiotic (drug A) was applied to the surface of Mueller-Hinton agar plates. The site at which the strip placed was marked on the plate and the plates were incubated for 1h at 37°C. Then the strip was removed and the other strip (drug B) was applied onto the imprint of strip A. The plates were incubated at 37°C for 24 h and then the MIC levels of each drug and combination were recorded.

Synergistic, additive, indifferent and antagonist effects of *A. baumannii* strains were evaluated by fractional inhibitory concentration (FIC) index for the combinations according to the following formula:

FIC index =FIC A (The MIC numerical value of A in the presence of B/The MIC numerical value of single A)+ FIC B (The MIC numerical value of B in the presence of A/The MIC numerical value of single B).

The combination was considered to be synergistic when the FIC index was ≤ 0.5; additive when > 0.5 but ≤ 1; indifferent when > 1 but ≤ 4; antagonistic when > 4[7].

Results

Of the 30 MDR *A. baumannii* strains tested, TIG, CO and DOR susceptibilities were 90%, 93.3%

and 50%, respectively. MIC50 and MIC90 values were 0.094 μg/mL and 0.19 μg/mL for CO; 2 μg/mL and 32 μg/mL for DOR; 0.38 μg/mL and 1.5 μg/mL for TIG, respectively (Table 1).

		MIC(μg/mL)		Susceptibility	Rate(%)
Antibiotic	**MIC Range**	**MIC_{50}**	**MIC_{90}**	**Susceptible**	**Resistant***
CO	0.023-8	0.094	0.19	93.3	6.6
DOR	0.50->32	2	>32	50	50
TIG	0.19-24	0.38	1.5	90	10

Table 1: MIC range, MIC_{50} , MIC_{90} values and susceptibility rates against clinically isolated MDR *A. baumannii* strains in ICUs.
* Intermediate strains are accepted as resistant.
MIC: Minimum Inhibitory Concentration; **MDR**: Multi Drug Resistant; **CO**: colistin; **DOR**: doripenem; **TIG**: tigecycline; **ICUs**: Intensive care units; ***A. baumannii*:** *Acinetobacter baumannii*.

The FIC values and the activities of antibiotic combinations are shown in Table 2.

The synergistic or additive effects were 9.9% for CO-DOR combination, 16.6% for CO-TIG combination and 13.3% for DOR-TIG combination, respectively. The antagonist effects were 6.6%, 16.6% and 33.3% for CO-DOR, CO-TIG and DOR-TIG combinations, respectively. Among the tested antimicrobial combinations, the combination of CO with TIG was the most effective against MDR A. baumannii strains isolated from the patients in ICUs (Table 3).

The synergistic or additive effects of DOR-TIG combination were 19.9% for DOR resistant strains and 6.6% for DOR susceptible strains. The antagonistic effect of DOR-TIG combination was 6.6% for DOR resistant strains and 60% for DOR susceptible strains.The synergistic or additive effects for DOR-TIG combination were higher in DOR resistant strains. The antagonistic effect was higher in DOR susceptible strains (Table 4).

The synergistic or additive effects of CO-DOR combination were 19.9% for DOR resistant strains and 0% for DOR susceptible strains.The antagonistic effect of CO-DOR combination was 6.6% for both DOR resistant and susceptible strains. The synergistic or additive effects for CO-DOR combination were higher in DOR resistant strains.The antagonistic effect did not differ from each other in DOR resistant or DOR susceptible strains for this combination (Table 5).

No	CO-DOR		CO-TIG		DOR-TIG	
	FIC	**Activity**	**FIC**	**Activity**	**FIC**	**Activity**
1	10,005	**ID**	1,376	**ID**	100,009,375	**ID**
2	1,000,375	**ID**	0,7545	**ADD**	1,001	**ID**
3	0,0321	**S**	0,1148	**S**	1,003	**ID**
4	131,607	**ID**	0,717	**ADD**	0,507	**ADD**
5	2,52	**ID**	0,846	**ADD**	4,02	**ANT**
6	2,031	**ID**	0,1562	**S**	0,0645	**S**
7	20,005	**ID**	3,12	**ID**	1,336	**ID**
8	1,012	**ID**	1,16	**ID**	1,521	**ID**
9	20,205	**ID**	5,404	**ANT**	1,015	**ID**
10	0,501	**ADD**	1,076	**ID**	0,759	**ADD**
11	0,6575	**ADD**	2,125	**ID**	1,003	**ID**
12	13,295	**ID**	1,986	**ID**	10,005	**ID**
13	10,005	**ID**	1,646	**ID**	1,002	**ID**
14	1,023	**ID**	1,829	**ID**	1,567	**ID**
15	1,000,375	**ID**	1,5	**ID**	1,001	**ID**
16	1,021	**ID**	1,512	**ID**	0,678	**ADD**
17	3,922	**ID**	4,666	**ANT**	2,125	**ID**
18	1,953	**ID**	3,473	**ID**	3,041	**ID**
19	3,927	**ID**	12,375	**ANT**	1,085	**ID**
20	8,086	**ANT**	12,6	**ANT**	1,521	**ID**
21	5,442	**ANT**	5,681	**ANT**	1,042	**ID**
22	1,528	**ID**	1,376	**ID**	6,19	**ANT**
23	1,341	**ID**	1,457	**ID**	6,38	**ANT**
24	1,337	**ID**	1,986	**ID**	5,283	**ANT**
25	1,352	**ID**	2,348	**ID**	5,39	**ANT**
26	1,012	**ID**	1,829	**ID**	4,072	**ANT**
27	1,337	**ID**	1,497	**ID**	5,45	**ANT**
28	1,335	**ID**	1,519	**ID**	4,19	**ANT**
29	1,341	**ID**	1,452	**ID**	4,072	**ANT**
30	1,341	**ID**	1,657	**ID**	4,072	**ANT**

Table 2: The FIC values and the activities of antibiotic combinations against 30 clinically isolated MDR *A. baumannii* strains in ICUs.
FIC: Fractional Inhibitory Concentration; **MDR**: Multi Drug Resistant; S: synergistic; **ADD**: additive; **ID**: indifferent; **ANT**: antagonistic; **CO**: colistin; **DOR**: doripenem; **TIG**: tigecycline; **ICUs**: Intensive care units; ***A. baumannii***: *Acinetobacter baumannii*.

To conclude, the synergistic or additive effects for both CO-DOR and DOR-TIG combinations were higher in DOR resistant strains.

Combination	Synergistic effect	Additive effect	Indifferent effect	Antagonistic effect
CO-DOR	1(3.3)	2(6.6)	25(83.3)	2(6.6)
CO- TIG	2(6.6)	3(10)	20(66.6)	5(16.6)
DOR-TIG	1(3.3)	3(10)	16(53.3)	10(33.3)

Table 3: Synergy test results for CO-DOR, CO-TIG and DOR-TIG combinations against MDR *A. baumannii* strains obtained from patients in ICUs.
Data presented as n(%) of bacterial strains.
CO: colistin; **DOR**: doripenem; **TIG**: tigecycline; **ICUs**: Intensive care units; **MDR**: Multi Drug Resistant; ***A. baumannii***: *Acinetobacter baumannii*; **ICUs**: Intensive care units.

DOR-TIG combination	Synergistic effect	Additive effect	Indifferent effect	Antagonistic effect
DOR resistant strains (15 strains)	1(6.6)	2(13.3)	11(73.3)	1(6.6)
DOR susceptible strains (15 strains)	0(0)	1(6.6)	5(33.3)	9(60)

Table 4: Synergy test results of DOR-TIG combination against DOR resistant and DOR susceptible *A. baumannii strains*.
Data presented as n(%) of bacterial strains
DOR: doripenem; **TIG**: tigecycline; ***A. baumannii*:** *Acinetobacter baumannii*.

CO-DOR combination	Synergistic effect	Additive effect	Indifferent effect	Antagonistic effect
DOR resistant strains (15 strains)	1(6.6)	2(13.3)	11(73.3)	1(6.6)
DOR susceptible strains (15 strains)	0(0)	0(0)	14(93.3)	1(6.6)

Table 5: Synergy test results of CO-DOR combination against DOR resistant and DOR susceptible A. baumannii strains.
Data presented as n(%) of bacterial strains
CO: colistin; **DOR**: doripenem; ***A. baumannii***: *Acinetobacter baumannii*

Discussion

A. baumannii has been recognized as a worldwide emerging cause of nosocomial outbreaks and is listed as one of the six top-priority dangerous microorganisms by the Infectious Diseases Society of America (IDSA)[11]. In the last two decades, A.baumannii has become an important nosocomial pathogen in Turkey, as well as throughout the world and is a leading problem in treatment. Carbapenems, quinolones, aminoglycosides and combinations with sulbactam are commonly used for the treatment of these infections. Unfortunately, resistance rates for these antibiotics are increasing[12].

Dizbay et al. investigated the antimicrobial susceptibilities of MDR *A.baumannii* strains isolated from ventilator-associated pneumonia for 12 different antibiotics. The resistance rates for imipenem(IMP) and meropenem(MEM) were 80.3% and 71.2%, respectively[13]. Tunyapanit et al. investigated the in vitro activities of IMP against 100 *A.baumannii* strains. They found the susceptibility rate as 45% for IMP. MIC50 and MIC90 values of IMP were 16 and > 32 μg/mL, respectively[14]. Due to increased resistance among *A.baumannii* strains against commonly used carbapenems, DOR being the newest carbapenem has become the drug of choice for clinicians.

However, resistance to DOR among *A.baumannii* has also increased. Cekin et al. determined the in vitro activities of DOR, IMP and MEM against 94 clinical *A. baumannii* isolates by E-test. IMP, MEM, DOR susceptibilities of *A. baumannii* isolates were found as 22.3%, 17.0% and 12.8%, respectively. MIC50 and MIC90 values were > 32 μg/mL for DOR[15]. In our study, of the 30 MDR *A. baumannii* strains tested, 50% were susceptible to DOR. MIC50 and MIC90 values were 2 μg/mL and > 32 μg/mL, respectively.

Increasing resistance among *A. baumannii* has led clinicians to seek new therapeutic alternatives. TIG is one of the new therapeutic alternatives for *A. baumannii*. TIG is the first representative of the glycylcycline class of antibacterial agents to be marketed for clinical use. The US Food and Drug Administration (FDA) has approved its use for complicated intra-abdominal and complicated skin and skin structure infections. In vitro testing with TIG has revealed potent antibacterial activity against a large number of disease, causing Gram-positive and Gram-negative aerobic bacteria and anaerobes, including *A. baumannii*[16,17]. TIG has provided hope for the treatment of *A. baumannii* infections including carbapenem resistant isolates. However, reduced susceptibility to TIG has recently been identified.

Dizbay et al. detected 8% resistance rate among 25 extensive drug resistant *A. baumannii* strains for TIG[7]. Karaoglan et al. analyzed 50 carbapenem-resistant *A. baumannii* strains and the susceptibility rate was detected as 64% for TIG[18]. Baadani et al. described the rates and patterns of TIG resistance

among A. baumannii isolates from 2 major hospitals in Riyadh Region over a 2-year period. TIG resistance rate was 9.7 among 1307 A. baumannii isolates[19].

Ahmed et al. tested 232 carbapenem resistant clinical isolates of *A. baumannii* and the 7.6% of the isolates were fully resistant to TIG (20). Similarly, in our study, of the 30 MDR *A.baumannii* strains tested, 10% resistance rate to TIG was determined. MIC50 and MIC90 values were 0.38 μg/mL and 1.5 μg/mL for TIG, respectively.

Another new therapeutic alternative for A.baumannii is CO. CO is rapidly bactericidal against Gram-negative bacteria, interacting with the lipid A moiety of lipopolysaccharide to cause disorganization of the outer membrane. CO has excellent bactericidal activity against most gram negative aerobic bacilli, including Acinetobacter species[11,21]. CO, as the last resort for treatment of MDR *A. baumannii*, has received much attention in recent years. Unfortunately, resistance to CO has been reported all over the world. CO resistant Acinetobacter spp. was first reported in Czech Republic in 1999. By then, the number of reports from all over the world increased year by year. The highest resistance rate was reported in Asia, followed by Europe[11].

Cıkman et al. evaluated the MIC values of 33 IMP resistant A.baumannii strains for CO by E-test. Of the 33 strains included in the study, 21 were resistant to CO. MIC50 and MIC90 values for CO were 8 μg/mL and 32 μg/mL, respectively[22]. Baadani et al. tested CO resistance among 1307 *A. baumannii* isolates. They detected CO resistance rate as 1.8% (19). Ahmed et al. evaluated 232 carbapenem resistant clinical isolates of A. baumannii . All isolates were susceptible to CO[20]. Karaoglan et al. analyzed antibiotic susceptibility of *A.baumannii* strains. Of the 50 carbapenem-resistant A.baumannii strains tested, 96% were susceptible to CO[18].

In our study, of the 30 MDR *A. baumannii* strains tested, 93.3% were susceptible to CO. We determined MIC50 and MIC90 values as 0.094 μg/mL and 0.19 μg/mL for CO, respectively.

The combinations of antibiotics acting by different mechanisms are used for the treatment of MDR *A.baumannii* strains in many studies. By using combinations of multiple drugs, bacterial resistance is likely to be reduced. The incidence of adverse drug responses is also likely to be reduced due to the use of lower drug doses[23]. In the present study, we investigated the combination therapy options for infections caused by MDR *A. baumannii* strains.

The synergistic activities of TIG and CO with each other and with DOR were investigated.

Karaoglan et al. evaluated 50 carbapenem-resistant *A. baumannii* strains by E-test method and CO-TIG combination therapy was found to be synergistic in 12% of the strains tested[18]. Dizbay et al. tested in vitro synergistic activity of CO-TIG combination for 25 A. baumannii strains isolated from ventilator-associated pneumonia by E-test method. They observed synergistic activity in 18 of 25 (72%) isolates for CO-TIG combination. No antagonism was detected in the study[7]. Principe et al. observed synergistic activity in 2 strains (8.3%) among 22 MDR *A. baumannii* strains for CO-TIG combination[24]. In the present study, CO-TIG combination was synergistic or additive against 5 (16.6%) of the tested strains.

Dinc et al. investigated the efficacy of DOR monotherapy versus DOR combination therapy with CO and TIG in experimental sepsis. A carbapenem-resistant *A. baumannii* was used to develop a sepsis model in 8-10 week old mice by intraperitoneal injection. The results of the study showed that combination therapies with DOR are more effective than monotherapy and the combination of DOR with TIG has more rapid bactericidal effect than that with CO[25].

In the present study, DOR-TIG combination (13.3%) was more synergistic or additive than DOR-CO combination (9.9%) for *A. baumannii* strains.The synergistic or additive effect of DOR-TIG combination was 19.9% for DOR resistant and 6.6% for DOR susceptible strains. The synergistic or additive effect of CO-DOR combination was 19.9% for DOR resistant and 0% for DOR susceptible strains. In other words, the synergistic or additive effects for both CO-DOR and DOR-TIG combinations were higher in DOR resistant strains.

Limited options in the treatment of MDR *A. baumannii* infections, has made the combination antibiotic therapy a strategy often used in the treatment. In the present study, the antimicrobial activities of combinations of different antibiotics have been studied with the aim of developing new therapeutic options for infections caused by MDR *A. baumannii*. The combination of CO with TIG was most effective among the tested antimicrobial combinations, against MDR *A. baumannii* strains isolated from patients in ICUs.The synergistic or additive effects for both CO-DOR and DOR-TIG combinations were higher in DOR resistant strains. This study suggested that combination therapy with DOR

for treating MDR *A. baumannii* infections, should be used especially in DOR resistant strains. All these data will help clinicians to determine the appropriate antibiotic combinations against infections caused by MDR *A. baumannii* strains.

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