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IN VITRO ACTIVITY OF COLISTIN IN COMBINATION WITH DORIPENEM AGAINST CARBAPENEM NON-SUSCEPTIBLE *ACINETOBACTER BAUMANNII*

Acinetobacter baumannii has become a major healthcare-associated pathogen worldwide in the last two decades [1].

A. baumannii is a Gram-negative opportunistic pathogen and one of the leading causes of hospital acquired infections such as septicaemia, ventilator-associated pneumonia (VAP), wound infections and urinary tract infections [2].

In recent years, treatment of infections caused *by Acinetobacter* species has become difficult due to the spread of multidrug-resistant (MDR) strains [3]. *Acinetobacter* could be resistant to all β-lactam antibiotics, aminoglycosides and quinolones. MDR *Acinetobacter* is defined as resistant to at least three classes of the following antibiotics: cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and β-lactam/β-lactamase inhibitors. Extensive drug-resistant (XDR) *Acinetobacter* is defined as resistant to all standard antimicrobial agents except colistin or tigecycline. Pandrug-resistant (PDR) *Acinetobacter* is defined as resistant to all categories of antimicrobial agents [4].

Several factors may lead to carbapenem resistance in *A. baumannii*, most importantly - the acquisition of carbapenem hydrolyzing β-lactamases. Other mechanisms include reduced expression of outer membrane proteins (OMPs), altered affinity or expression of penicillin-binding proteins (PBPs) and multidrug efflux pumps [5].

The capacity of *A. baumannii* to develop multiple mechanisms of resistance to various antibiotic classes predicts that antibiotics will soon be unavailable to treat serious MDR *A. baumannii* infection [6]. So there is an urgent need to enforce new therapeutic options, infection control measures and antimicrobial stewardship programs [7].

The development of resistance to carbapenems has increased the use of polymyxins and tigecycline. They are considered the last resort of treatment for MDR *A. baumannii* [8]. However, emergence of resistance to them during treatment of *A. baumannii* infections has been reported [9].

Colistin (Polymyxin E) is a cationic antibiotic, which is bactericidal for Gram-negative bacteria, interacting with lipid A causing disarrangement of the outer membrane [10]. Polymyxins have lost favour in treating infections secondary to toxicities associated with

higher doses [11, 12]. However, the high success rates of combination treatments in cases of possible resistance against colistin and in carbapenemase-producing Gram-negative bacterial infections, have resulted in increased use of colistin in combination with other antibiotics [13].

Various combination treatment approaches have been proposed through *in vitro, in vivo* and clinical studies [14, 15]. Antibiotic combinations including, ampicillin/sulbactam, imipenem, rifampin, tigecycline, vancomycin and fosfomycin have shown effectiveness against MDR *A. baumannii* [16-19].

Doripenem is a newly marketed carbapenem with an *in vitro* activity against Gram-positive, Gram-negative, and anaerobic microorganisms and is also more stable against carbapenamases than other carbapenems. Thus, doripenem has been considered a valuable addition to the options available for the treatment of serious MDR bacterial infections [20, 21].

Colistin combination with other antibiotics looks promising. Combination therapy limits bacterial resistance, decreases antibiotic toxicity and leads to synergy [22-24].

Material and Methods. Bacterial Isolates. Thirty-two isolates of *A. baumannii* were collected from different clinical specimens including respiratory secretions, pus, blood and urine that were referred to the Microbiology Laboratory at TBRI. Samples were collected from outpatient clinic attendants as well as hospitalized patients from different departments including the ICU, surgery, urology, gastroenterology and nephrology during the period from November 2014 to December 2015. Isolates were diagnosed and identified using the API 20 E system (Bio-Mérieux, France) and were then confirmed by using VITEK® 2 Compact System (Bio-Mérieux, France).

Antimicrobial susceptibility testing. The antibiotic susceptibility of the isolates was tested by VITEK-2 Compact using (AST-N222) cards in compliance with CLSI 2017 guidelines. The antibiotics tested were: piperacillin, piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin, minocycline, colistin, trimethoprim/sulfamethoxazole. Tigecycline susceptibility was done by using Kirby-Bauer Disk Diffusion (KBDD). Tigecycline (TGC; 15µg) disks *(Bio-Rad, USA)* were used and the Interpretation of the isolates' susceptibility was detected according to Torrico et al. [25] who reported the FDA disk diffusion zone diameter susceptibility and resistance breakpoints.

Antimicrobial agents and MIC determination. Minimum Inhibitory Concentrations (MICs) of doripenem were tested by using E-test. Breakpoints were interpreted according to CLSI [26]. Escherichia coli ATCC 25922 was used as a quality control strain. MIC of colistin was determined by agar dilution method according to Hanlon et al, and CLSI [27, 28]. Colistin antibiotic powder (LKT Laboratories, USA) with biological potency of 19366 U/mg was obtained. Stock solutiosn of 10,000µg/ml, 1,000µg/ml and 100µg/ml for colistin

were prepared and were stored at - 70° C. Solutions with different concentrations were prepared on the day of the experiment.

Synergy Testing. Antimicrobial interaction testing was performed by agar dilution-E-test method as described by Sopirala et al. [29]. Testing the antimicrobial agents in combination was dependent on previous determination of the MICs of colistin by agar dilution method and doripenem by E-test strips. The antibiotic with the lowest MIC was considered the most active drug. The most active drug (colistin) was incorporated into Muller Hinton agar (MHA) (MAST Diagnostics, UK). The plates incorporated with colistin at one-half and one-fourth the MIC, were inoculated with 0.5 McFarland suspensions for each isolate. The E-test strip of doripenem was applied on each MHA plates of both concentrations for each tested isolate. Following incubation for 24 hours at 37°C, the strips were read and the reading of E-test MIC was compared to that performed in absence of colistin. The interpretation was done as described by Pongpech et al. [30] by determination of Fractional Inhibitory Concentration Index (FICI) as the FIC of drug A + FIC of drug B. FIC of drug A = MIC of drug A in combination/MIC of drug A alone. FIC of drug B = MIC of drug B in combination/MIC of drug B alone. Results interpreted as follows: synergy if FICI < 1, additative if FICI = 1 and antagonism if FICI > 1.

Phenotypic detection of MBL production. All carbapenem non-susceptible *A. baumannii* isolates were subjected to MBL E-test to test for MBL production. An overnight culture of the clinical isolate was diluted in saline to a turbidity of a 0.5 McFarland standard. A cotton swab was used to transfer the inoculum onto a MHA plate. Once dried, an E-test MBL strip (Bio-Mérieux, France) was applied onto the plate which was then incubated at 37° C for 16 to 18 hours to detect the presence of metallo enzymes. The E-test MBL strip contains a double sided seven-dilution range of Imipenem (IP) (4 to 256 µg/ml) and Imipenem (1 to 64 µg/ml) in combination with a fixed concentration of EDTA (IPI). A reduction in MIC in the presence of EDTA of greater than or equal to eight-fold (IP/IPI ≥8) or a phantom zone between IP/IPI or deformation of either ellipse is interpreted as positive for MBL activity.

Statistical analysis. Results were expressed as mean, range, number and percent. Statistical Package for Social Sciences (SPSS) computer program (version 19 windows) was used for data analysis. Comparison between categorical data [number (%)] was performed using either Chi-square test or Fisher Exact test whenever it was appropriate. P value of < 0.05 indicates significant results.

Results. Specimens and Isolates Collected. The majority of the isolates (10/32, 31.25 %) were equally recovered from urine, respiratory samples and pus specimens. Two isolates were recovered from blood and central venous catheter. Regarding specimen source, most of the isolates were recovered from inpatient (30/32; 93.75 %) compared to outpatient (2/32; 6.25 %) with a highly significant difference (P=0.001). ICU was the main source of specimen recovery with isolation rate (9/32; 28.13 %) followed by the Urology

and Surgery units (8/32; 25 %), Gastroenterology Unit (3/32; 9.37 %) and Nephrology Unit (2/32; 6.25 %).

The distribution *A. baumannii* isolates according to gender showed that 19 (59.37 %) of the isolates were recovered from males and 13 (40.63 %) were recovered from females with no significant difference ($p > 0.05$). The age range was from 30 to 83 years with a mean of 53.56 years.

Antimicrobial Susceptibility Testing. All isolates (100 %) were resistant to meropenem and (31/32; 96.87 %) were resistant to imipenem. All isolates (100 %) were resistant to piperacilin, piperacillin/tazobactam and cefipime, followed by ceftazidime (31/32; 96.87 %), ciprofloxacin (31/32; 96.87 %) and trimethoprim-sulphamethaxole (29/32; 90.63 %). Most of the isolates (26/32; 81.25 %) were resistant to gentamycin followed by amikacin (20/32; 62.50%) and tobramycin (21/32; 65.63 %). Most of the isolates were sensitive to tigecycline (29/32; 90.63 %) and colistin (30/32; 93.75 %) followed by minocycline (17/32; 53.13 %) (table 1).

Antibiotics	*A. baumannii* isolates N=32		
	Sensitive N (%)	Intermediate N (%)	Resistant N (%)
Imipenem	0(0.00)	1(3.13)	31(96.87)
Meropenem	0(0.00)	0(0.00)	32(100)
Ceftazidime	1(3.13)	0(0.00)	31(96.87)
Cefipime	0(0.00)	0(0.00)	32(100)
Piperacillin/tazobactam	0(0.00)	0(0.00)	32(100)
Piperacilin	0(0.00)	0(0.00)	32(100)
Amikacin	8(25.00)	4(12.50)	20(62.50)
Gentamycin	5(15.62)	1(3.13)	26(81.25)
Tobramycin	4(12.50)	7(21.87)	21(65.63)
Ciprofloxacin	1(3.13)	0(0.00)	31(96.87)
Minocycline	17(53.13)	12(37.50)	3(9.37)
Colistin	30(93.75)	0(0.00)	2(6.25)
Trimethoprim-Sulphamethaxole	3(9.37)	0(0.00)	29(90.63)
Tigecycline	29(90.63)	3(9.37)	0(0.00)

Table 1. Susceptibility profile of *A. baumannii* isolates to the tested antibiotics.

MIC of colistin was determined by using E-test, VITEK 2 Compact system and agar dilution methods. The results of susceptibility pattern and MICs ranges, MIC_{50} & MIC_{90} of colistin tested by the three previous methods are shown in tables 2, 3.

Colistin susceptibility (N=32)	VITEK 2	E-test	Agar dilution method
Sensitive N (%)	30 (93.75)	32 (100)	9 (28.13)
Resistant N (%)	2 (6.25)	0(0.00)	23 (71.87)

Table 2. Colistin susceptibility by E-test, VITEK 2 Compact system and agar dilution methods.

Methods	Carbapenem non-susceptible *A. baumannii* isolates		
	MIC range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Agar dilution	1-8	4(R)	4(R)
VITEK 2	0.5-4	0.5(S)	2(S)
E-test	0.023-0.125	0.094(S)	0.125(S)

R: resistant; S: sensitive.

Table 3. MICs ranges, MIC_{50} & MIC_{90} of colistin tested by E-test, VITEK 2 compact system and agar dilution methods.

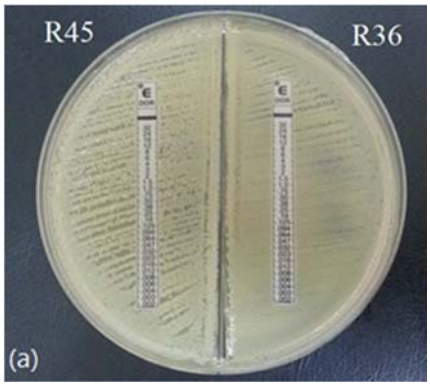
On comparing E-test and VITEK 2 with the agar dilution results, we found that both of them produced errors when *A. baumannii* was tested for colistin MIC. E-test showed 23 very major errors (72 %) while VITEK 2 Compact system produced 22 very major errors (69 %) and one major error (3 %). When the results were evaluated upon the acceptable performance criteria for susceptibility tests; the E-test and VITEK 2 Compact system performed high very major error rates in detecting colistin susceptibility with lack of agreement between both tests and agar dilution method (table 4).

* Kappa value shows lack of agreement between the two tests.

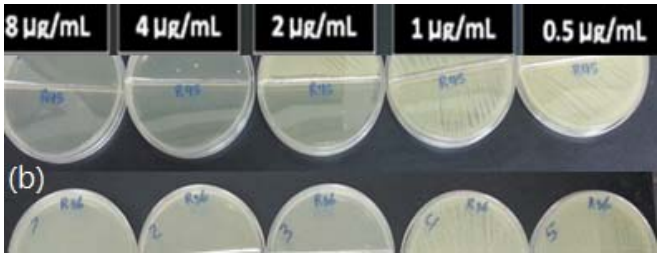
Table 4. Comparing MIC values of colistin by E-test and VITEK 2 Compact system to the agar dilution method.

Tests used for MIC detection		Agar dilution method		Kappa value
		Resistant (N=23)	Sensitive (N=9)	
E-test	**Resistant** (N=0)	0 (0.00%)	0 (0.00%)	0
	Sensitive (N=32)	23 (100.0%)	9 (100.0%)	
Vitek2	**Resistant** (N=2)	1 (4.34%)	1 (11.11%)	-0.040*
	Sensitive (N=30)	22 (95.65%)	8 (88.88%)	

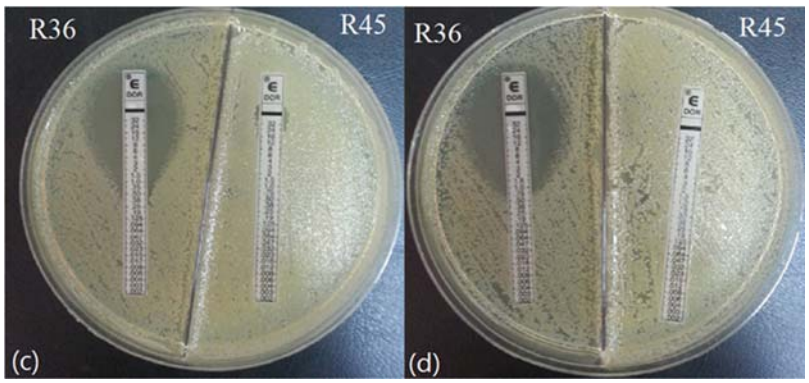
Synergy Results. Interaction testing for colistin and doripenem was performed using agar dilution-E-test method. Each isolate was tested with colistin plus doripenem at both 1/2 and 1/4 MIC of colistin (Figure 1).



(a): Doripenem E-test: showing resistant isolates (R45, R36) with MIC ≥ 32µg/ml.



(b): Serial agar dilutions of CS: showing MIC of isolates (R45, R36) at 2 µg/mL.



(c): R36 and R45 isolates at 1/2 MIC of CS with DOR E-test: showing synergy and antagonism with FICI of 0.515 and 1.5; respectively.

(d): R36 and R45 isolates at 1/4 MIC of CS with DOR E-test: showing synergy and antagonism with FICI of 0.273 and 1.25; respectively.

Figure 1. Agar dilution E-test method showing synergy versus antagonism between colistin (CS) and doripenem (DOR) in two *A. baumannii* isolates.

Results of combination testing showed reduction in doripenem MIC values on using both 1/2 MIC and 1/4 MIC of colistin in 27/32 (84.37 %) and 23/32 (71.87 %); respectively denoting synergy (FIC <1) between the 2 drugs. Antagonism was detected on using 1/2 and 1/4 MIC of colistin in 5/32 (15.63 %) and 9/32 (28.13 %); respectively. Synergy was detected in 23/32 (85.19 %) of the isolates at both used concentrations with good agreement between both concentrations. No isolates gave additive effect at both MIC values (table 5).

Antimicrobial Combination	Synergy (FIC <1) N (%)	Additive (FIC=1) N (%)	Antagonism (FIC >1) N (%)	Kappa value	P value
1/2 MIC of CS+DOR	27/32(84.37)	0(0.00)	5/32(15.63)	0.642*	0.001**
1/4 MIC of CS+DOR	23/32(71.87)	0(0.00)	9/32(28.13)		

*Kappa value indicates good agreement.

** P value ≤ 0.05 is considered significant.

Table 5. Results of interaction testing of colistin (CS) with doripenem (DOR) against carbapenem non-susceptible *A. baumannii* isolates.

There were 23 isolates that showed resistance to both colistin (by agar dilution) and carbapenems. The tested combination therapy exhibited synergy in (21/23; 91.30 %), (20/23; 86.96 %) of these isolates when 1/2 and 1/4 MIC of colistin were used; respectively with good agreement (p=0.001). Synergy was detected in 20/23 (95.24 %) of the isolates

at both concentrations. Antagonism was detected in (2/23; 8.70 %) and (3/23; 13.04 %) of the isolates when 1/2 and 1/4 MIC of colistin were used; respectively.

Phenotypic Detection of MBL. MBL IP/IPI E-test strips showed that 24/32 (75 %) of carbapenem non-susceptible *A. baumannii* isolates were MBL positive while 8/32 (25 %) of isolates were MBL negative. MBL production was detected in 24 isolates (75 %); 19/24 (79.16 %) of these isolates showed synergy and 5/24 (20.83 %) showed antagonism when 1/2 MIC of CS+DOR combination was used, while 16/24 (66.66 %) of these isolates showed synergy and 8/24 (33.33 %) showed antagonism when 1/4 MIC of CS+DOR combination was used with no significant difference (table 6) indicating that there is no association between the synergy results detected at both concentrations and MBL status.

Carbapenem non-susceptible isolates (N=32)	Synergy (FICI <1)		Antagonism (FICI >1)		P value (at 1/2 MIC)	Pvalue (at 1/4 MIC)
	1/2 MIC of CS+DOR	1/4 MIC of CS+DOR	1/2 MIC of CS+DOR	1/4 MIC of CS+DOR		
MBL positive (N=24)	19/24 (79.16%)	16/24 (66.66%)	5/24 (20.83%)	8/24 (33.33%)	0.160*	0.256*
MBL negative (N=8)	8/8 (100%)	7/8 (88.50%)	0 (0.00%)	1/8 (12.5%)		

*P value ≤ 0.05 is considered significant.

Table 6. Results of interaction testing in relation to MBL status.

Discussion. *Acinetobacter baumannii* rapidly acquires extensive drug resistance with a high morbidity and mortality rates of approximately 30 %. It has become a major concern to the medical community due to limited therapeutic options and challenges for infection control [31, 32].

The aim of the present study is to detect the isolation rate of carbapenem non-susceptible *A. baumannii* isolates over a period of one year in TBRI tertiary hospital located in Giza, Egypt and to test the *in vitro* activity of combination therapy of colistin with doripenem as a potential treatment option for carbapenem resistant MDR *A. baumannii* isolates.

In the present study, 32/54 (59 %) isolates of *A. baumannii* were carbapenem non-susceptible. This result is alarming as it suggests the emergence of carbapenem-resistant *A. baumannii* in our facility with its potential to become a major cause of nosocomial infections.

Comparable results were reported from Egypt by Fattouh and Nasr El-din. [33] where carbapenem resistant A.baumannii accounted for 71.4 %. Those results were lower than

those reported from Morocco (77.4 %) and India (71.3 %) but higher than what was reported from Qatar (57.3 %) and Iran (48 %) [34-37].

Acinetobacter baumannii cause various infections such as pneumonia, UTIs, septiceamia, meningitis and wound infections in immune-compromised patients [38]. In the current study, *Acinetobacter* isolates were recovered from different clinical samples. Categorization of clinical *Acinetobacter* infection sources showed that they were equally isolated from urine, respiratory and pus samples (31.25 %). A recent Egyptian study conducted in Alexandria University Hospital showed that respiratory tract infection represented 60 % of *A. baumannii* infections [39].

Our results were comparable with other studies where *Acinetobacter* isolates were mainly recovered from respiratory specimens and ranged from 32-64 % [40-43, 37]. However, other studies reported higher rates of isolation from sources other than respiratory samples. A study from Egypt conducted by Gamal El-Din [44] revealed that most of the Acinetobacter isolates (53.3 %) were recovered from wound infection followed by respiratory tract infections (30 %). Sivaranjani et al. [35] showed that most isolates were from pus samples (38.52 %) followed by endotracheal aspirates (20.49 %). Most of et al. [45] showed high isolation rate (38 %) from blood.

The previous results were comparable to our study where respiratory tract, urinary tract and soft tissue infections were the most common sites of infection. This could be related to the various predisposing factors and to the type of interventional procedures patients were exposed to.

In our study the vast majority of the *Acinetobacter* isolates (94 %) were obtained from inpatients at TBRI hospital, 28.13 % of which were recovered from the ICU, followed by the urology and surgery departments (9.37 % for each). Such results were in agreement with other studies where the majority of *A. baumannii* were isolated from the ICU (73.3 %) in Egypt, (54.9 %) in Morocco**,** (56 %) in Saudi Arabia and (72 %) in Sudan [44, 42, 43, 37].

These findings support the concept that *A. baumannii* is the ICU superbug as many risk factors associated with *A. baumannii* infection exist in the ICU such as immune-compromised persons, longer duration of stay in hospitals, invasive devices use on patients, the broad spectrum antibiotics therapy, possible and frequent contaminations and cross transmission of this bacteria through environmental reservoirs and hands of healthcare workers [46, 32, 43].

In the community, *A. baumannii* has been found to be associated with community acquired pneumonia in Asia and Australia although rare in USA [47]. In the present study the isolation rate of *A. baumannii* from the outpatient clinics was 6 % from pus samples. Another study conducted in Sudan reported also a lower rate of 4 %. Such finding suggests that monitoring antibiotic susceptibility of bacteria isolated from the community appears to be mandatory [43].

The present study showed that *A. baumannii* infections were more predominant in males (19/32; 59.37 %) than females (13/32; 40.63 %); however, no significant difference was shown. These results were comparable with other studies which stated that 53 % to 74.2 % of affected patients were male but the reason is not justified [48, 49, 32, 50]. However, a study from Saudi Arabia conducted by Abdalhamid et al. [42] reported that 46 % patients were males and 54 % were females. Another study conducted by Sivaranjani et al. [35] showed no gender difference in *A. baumannii* infections.

The age range of distribution of *A. baumannii* isolates in our study was from 30 to 83 years, with a median of 52. Our results are comparable to the results of Uwingabiye et al. [37] and Abdalhamid et al. [42] where the average age of patients was 54 and 46 years, respectively. However, the old age of patients was recognized as an independent risk factor of the acquisition of *A. baumannii* infection [51].

As noted, most of our epidemiologic findings are consistent with several reports worldwide; *A. baumannii* infection occurred in the elderly, mainly male patients and affecting critically ill especially those admitted into the intensive care units [52, 40, 53, 54].

In the current study, resistance was high to almost all groups of antibiotics, 100% of the isolates were resistant to meropenem and 96.87 % were resistant to imipenem. All isolates (100 %) were resistant to piperacilin, piperacillin/tazobactam and cefipime, followed by ceftazidime (96.87 %), ciprofloxacin (96.87 %), amikacin (62.5 %) and trimethoprim-sulphamethaxole (90.63 %). A study from Egypt showed a relatively similar resistance pattern of 52 isolates to: imipenem (96.2 %), meropenem (76.9 %), ciprofloxacin (100 %), amikacin (76.9 %), cefipime (80.8 %) and ceftazidime (100 %) [55]. Another study from Egypt showed that *A. baumannii* isolates were 100% resistant to amoxicillin–clavulanate, third- and fourth-generation cephalosporins, and monobactams; however, lower resistance rates to ciprofloxacin (85 %) and amikacin (45 %) were detected [56].

In our study, the resistance rate against ceftazidime was 96.87%. Lower resistance rates of 80 %, 66.7 % and 61.82 % were reported from other studies from Egypt by Gamal El-Din. [44], Fattouh and Nasr El-din. [33] and Daef et al. [57]; respectively. Other studies conducted in the United States, South Africa and Aisa reported resistance rates of 52.1%, 68.4%, 60%-92.1%; respectively toward ceftazidime [40, 58, 59, 60]. In the present study, 100% of the isolates were resistant to cefepime. This was similar to the finding of Al-Agamy et al. [56]. However, a study from Egypt conducted by Gamal El-Din [44] showed lower a resistance rate of 63.3 %. Kulah et al. [61] from Turkey reported also low resistance to cefipime (34.8 %). The resistance of *A. baumannii* to extended-spectrum cephalosporins is usually related to the over-expression of the resident Ambler class C bla_{ADC} gene or infrequently to the acquisition of ESBL encoding genes [56].

For the aminoglycosides in our study, amikacin was the most effective with a resistance rate of 62 %, 66 % for tobramycin and 81 % for gentamycin. This was relatively in agreement with other studies from Egypt where they recorded resistance to

aminoglycosides of 63.3 % and 56.48 % [44, 57]. On the other hand, slightly higher rates were recorded in India where resistance to tobramycin, gentamicin and amikacin were 80 %, 85 % and 90 % respectively [40]. In Morocco, lower rates of resistance of 43 % for tobramycin and 52 % for amikacin were recorded [37]. The aminoglycosides resistance in *A. baumannii* involves the production of aminoglycosides modifying enzymes and genes encoding these enzymes can be acquired through plasmids, transposons or integrons [40, 32].

For quinolone, the resistance rate of ciprofloxacin in our study was 96.87 %. Similarly, high rate of 85 % was demonstrated from other study from Egypt [56]. A vast variety of results have been reported regarding ciprofloxacin resistance worldwide, but generally concluded high resistance pattern ranging from 66 % to 92.6 % [62, 63, 37]. Resistance of *A. baumannii* to quinolones is often caused by modifications in the structure of DNA gyrase secondary to mutations in the quinolone resistance-determining regions of the *gyrA* and *parC* genes. These changes result in a lower affinity for the binding of the quinolone to the enzyme-DNA complex [64, 65].

For trimethprim-sulfamethoxazole, we reported high resistance rate of 90.63 % against *A. baumannii*. Such finding was in agreement with a study from Egypt conducted by Gamal El-Din [44] where resistance rate was 83.3 %.

Tetracyclines particularly the second generation (minocycline) may offer good therapeutic options for MDR *A. baumannii*. This has been shown in our study which reported low resistance rate of 9.37 %. However, high resistance rates of 35 % and 52.6 % to minocycline have been reported in Iran [66, 67]. Minocycline has been described as the second most active agent after colistin. The interest in minocycline has increased due to its ability to overcome many tetracycline resistance mechanisms (most notably *TetA*). Its favorable safety profile, lack of needed dose adjustments for renal and hepatic failure, its ability to achieve good serum and tissue levels as well as to display bactericidal activity has allowed its more widespread use against MDR *Acinetobacter*. However, further studies are needed to assess if minocycline monotherapy is sufficient or whether it should be utilized as part of a combination therapy [68].

Carbapenems remain one of the most important therapeutic options for *A. baumannii* infections despite the fact that carbapenem-resistant strains are increasing [69]. Resistance to carbapenems is sufficient to define an isolate of *A. baumannii* as MDR [70].

Different carbapenem resistance rates have been stated globally. The resistance rate of *A. baumannii* to carbapenems was found to be 47.9 % in Algeria, 45 % in Tunisia, 89.6 % in India, 44.7 % in United States and 61.3% in Saudi Arabia [71, 72, 40, 59, 73]. The most prevalent mechanism of carbapenem resistance in *A. baumannii* is the enzymatic degradation by carbapenem- hydrolyzing –β-lactamases. The most widespread carbapenemases in *A. baumannii* are CHDLs and to a lesser extent, MBL and class A

carbapenemase. The impermeability associated with mutations altering the expression of porins and efflux pumps may also play a role [70, 56, 32].

Colistin and tigecycline have emerged as alternative treatment choices for carbapenem non-susceptible *Acinetobacter* infections. Concerning tigecycline, 9 % (3/32) of our isolates were non-susceptible. Comparable results were revealed by Tan et al. [75] and Baadani et al. [76] who reported 7.9 % and 9.7 % resistance rates; respectively. Lower resistance rate of 3.6 % was reported by Samawi et al. [77]. However, tigecycline is not recommended in treatment of VAP due to low lung penetration and rapid emergence of resistance [78, 79].

These data suggest that tigecycline can be used as a good therapeutic option against MDR *A. baumannii* isolates in our hospital; however, resistance rates should be monitored closely.

Detection of colistin resistance is currently debatable. In our study we used agar dilution method for colistin susceptibility and compared it to E-test and VITEK 2. Disk diffusion was not used to test colistin suseptiblity in our study as colistin diffuses poorly in the agar producing small inhibition zones resulting in poor differentiation of susceptible and resistant isolates [80]. Dilution methods remain the gold standard, but they are difficult to perform as routine tests in many clinical laboratories. Studies have reported that good concordance was found between agar dilution and broth micro dilution [81, 82, 83]. In the current study, it was noticed that suseptiblity to colistin was 100 % by E-test, 94 % by VITEK 2 and only 28 % by agar diution method. Tan and Ng [84] reported that VITEK 2 was unreliable for detecting colistin resistance, and results obtained by E-test may require confirmation by a standard MIC susceptibility testing method.

It has also been suggested that E-test results should be confirmed by a dilution method, especially when colistin use is required for the treatment of serious systemic infections caused by *A. baumannii* [85]. Similar to our results, Lee et al. [86] found good categorical agreements between VITEK 2 and E-test (both 99.1 %) compared to the agar dilution reference method.

In the current study, resistance to colistin was found in 72 % by agar dilution method. This result was comparable to a study done in Greece where colistin resistance was detected in (18/20, 90 %) of isolates by both agar dilution and broth micro-dilution methods [83].

Increased prevalence of colistin resistance in *Acinetobacter* isolates has been reported throughout the world, with a great variability in the occurrence in different geographic areas. The highest resistance rate was reported from Asia-Pacific followed by Europe, Americas and Africa. Reports from Asia, Europe, North America and South America also noticed recent increase of colistin-resistant *A. baumannii* ranging from 7 % to 40.7 % [14, 79, 87, 88].

Other studies reported lower resistance rates where colistin resistance ranged from 1.7 % to 15.2 % [44, 63, 50, 37]. However, resistance in Northern Europe and Northern Asian countries has not been reported yet [89].

These differences in the results of susceptibility to colistin could be explained by the difference in working environments and strategies of antibiotic consumption. Prevalence studies are required to observe the true resistance pattern of isolates [90].

The mechanism of resistance to colistin is rare and may be explained by the loss of lipopolysaccharide and/or deployment of a system of two-component regulatory system PmrAB [91, 92].

Another mechanism of resistance is expression of plasmid-mediated colistin resistance *mcr-1*. It is a member of the phosphoethanolamine transferase enzyme family which results in the addition of phosphoethanolamine to lipid A thus leading to colistin resistance. It has first been described in *Enterobacteriaceae* isolated from animals, food and human beings in China. Afterwards it has been reported in other countries in Asia, Europe and North America. Recent reports from Egypt further denote the dissemination of this mechanism due to the use of colistin in feeding animals [93, 94].

MBL production was considered uncommon in *Acinetobacter* but it is now emerging as a main mechanism of carbapenem resistance. Their hydrolytic activities toward carbapenems are significantly more potent than OXA-type carbapenemases (100- to 1,000-fold) Several types have been described like IMP-1, IMP-2, IMP-4, IMP-5, IMP-6, and IMP-11 [70, 30].

It is noteworthy to mention that the majority of our isolates showed resistance to important groups of antibiotics including third generation cephalosporins, aminoglycosides and quinolones which is a characteristic of MBL producing isolates. The same results were observed by Mohanty et al. [95] who reported a higher prevalence of resistance in MBL positive *A. baumannii* isolates as compared to the MBL-negative ones for all antibiotics except colistin. Since MBLs genes are carried on plasmids, this may explain the higher prevalence of co-resistance to other antibiotics found in MBL-positive isolates [96].

The MBL E-test has been suggested to be a sensitive method for detection of MBL production in *Acinetobacter* [97].

MBL activity was detected in (24/32; 75 %) of our isolates. Although these results were not confirmed by molecular methods, it correlates with the recent data of MBLs emergence (specifically the NDM-like) in the isolates from other studies from Egypt accounting for 59/150 (39.3 %) and 1/40 (2.5 %) [98, 99]. Our results are comparable to Karthika et al. [100] and Anwar et al. [101] who recorded MBL production in 70.9 % and 65.5 %; respectively. However, lower rate of 10 %, 55.7 %, 45 % were recorded from Egypt and other regions like India and Iran [44, 102, 103].

The increased rate of MBL detection in our study could be due to the fact that only colistin resistant isolates were screened. Another cause is the presence of OXA enzymes

whose enzymatic activity was found to be partially inhibited with chelator agents like EDTA [104].

Combination antibiotic therapy is a strategy often employed in the treatment of MDR *A. baumannii*. This approach attempts to achieve synergy [105]. Colistin combination treatment is useful for preventing antibiotic resistance and reducing toxicity [106]. Many *in vitro* studies supported the role of combination therapy with colistin in particular with carbapenems [107, 108, 14].

Doripenem, the latest broad-spectrum carbapenem approved in the United States, is more stable against carbapenemase than other carbapenems. Many previous studies have shown doripenem to be an effective treatment option since (i) it has potent *in vitro* activity against many Gram-negative and -positive bacteria (ii) lower propensity to select for resistance (iii) safe tolerability profile with lower seizure potential than imipenem and (iv) extended solution stability at room temperature [109].

In our study, all isolates (100 %) were resistant to doripenem with both MIC 50/90 of 32 µg/ml. Comparable results were found by Mustafa et al. [110] and Gilani et al. [111] where resistance to doripenem was 83 % and 76.7 %; respectively and MIC 50/90 were 32µg/ml for both studies. Doripenem was also shown to be not effective against 77.4 % of A. baumannii in a study conducted in Saudi Arabia by Somily et al. [112]. On the other hand, a study conducted by Dong et al. [113] in Taiwan showed that 56 % of *A. baumannii* were susceptible to doripenem and the MIC 50/90 were 0.38/32 µg/ml respectively.

Colistin and doripenem combination was tested in the current study using agar dilution/E-test method. Each isolate was tested with colistin plus doripenem at both 1/2 and 1/4 MIC of colistin. The agar dilution E-test method was used in our study as it correlated well with time-kill analysis; a methodology that is widely used to assess synergy between antibiotics. In addition, it was easier to perform, less time-consuming, and less expensive [29].

The main finding of this study was the synergistic effect of colistin-doripenem combination against carbapenem and colistin non-susceptible *A. baumannii* clinical isolates. Between the two concentrations evaluated, combination at 1/2 MIC of colistin and doripenem appeared to be most effectively synergistic (27/32; 84.37 %) than 1/4 MIC of colistin and doripenem (23/32; 71.87 %), with significant statistical difference between two concentrations (p value= 0.001). Therefore, antibiotic combinations were found to be superior to monotherapy in our study. These results were in agreement with two studies, one from USA conducted by Oleksiuk et al. [114] where the combination of colistin doripenem was synergistic and bactericidal against 72 % of *A. baumannii* isolates using time kill assays. The other one was from Korea conducted by Park et al. [115] that showed colistin/doripenem synergy rate of 53.7 % in XDR *A. baumannii* isolates compared to other antibiotic combinations including tigecycline/colistin (43.9 %) and tigecycline/doripenem (14.6 %).

The synergistic activity could be explained by the fact of the ability of colistin to disrupt the Gram-negative outer membrane thus increasing its permeability which may allow greater access of doripenem to the critical penicillin-binding proteins located on the cytoplasmic membrane, where the carbapenems act [116, 117].

However, Dinc et al. [109] reported that the colistin/doripenem combination was not more effective than other combinations in an *in vivo* study. Different synergy rates between various studies may be attributed to differences in sample size, regional epidemiologic features, testing methods used, differences in the concentrations of drugs and interpretation criteria for the synergy. Appropriate comparison of the synergy rates in different studies requires the establishment of a standard protocol, including common interpretation criteria [118].

In the current study, antagonism was detected for doripenem-colistin combination (5/32; 15.63 %) and (9/32; 28.13 %) at 1/2, 1/4 MIC respectively. In contrast, antagonism was not detected against *A. baumanii* isolates with the colistin/doripenem in other studies. The underlying cause of the antagonism demonstrated in the use of combinations of antibiotics against *A. baumannii* isolates has not been clearly identified [119, 114, 115].

On examining the synergy results regarding the MBL status, we found that synergy was high regardless of MBL activity, while Pongpech et al. [30] suggested that high synergy may be linked to the absence of MBL activity. Further evaluation is required on larger sample size and confirmation with molecular methods is recommended.

To date, studies of combination therapy have focused almost exclusively on colistin-susceptible XDR *A. baumannii*; however, the relevance of these data among colistin-resistant strains is unknown. In our study, we identified high rates of synergy (21/23; 91.30 %) and (20/23; 86.96 %) when colistin was combined with doripenem at 1/2, 1/4 MIC of colistin respectively against colistin-resistant *A. baumannii*. Our results agreed with Oleksiuk et al. [114] who reported bactericidal effect against 5/9 (56 colistin-resistant *A. baumannii* isolates.

A significant amount of time and energy has been devoted to studying combination therapy for the treatment of *A. baumannii* infection. Much of the current information is derived from *in vitro* or animal studies However, the results obtained from *in vitro* studies still need to be supported by further *in vivo* studies before they are used in clinical practice [118].

Conclusions. Carbapenem resistant *A. baumannii* is emerging as an important pathogen at TBRI. High rate of carbapnem resistant *A. baumannii* may reflect excessive use of carbapenems in our hospital setting. Tigecycline and minocycline are good therapeutic options for treatment of carbapnem resistant *A. baumannii*; however, monitoring for emergence of resistance is mandatory. The increase of colistin resistance in our *A. baumannii* isolates is alarming and requires further molecular investigation. Doripenem, which has been suggested to be a new option for treatment of infections

caused by MDR organisms, is not effective as monotherapy. Combination regimen of colistin with doripenem is superior to monotherapy and could be a promising therapeutic option for clinicians while considering optimal treatment options for MDR *A. baumannii* infections.

Recommendations. Patients should be screened for carbapenem resistant *A. baumannii* at hospital admission to minimize the inappropriate use of antibiotics. Use of carbapenem should be monitored to decrease antibiotic selective pressure and emergence of resistance. Minocycline was found to be effective in *A. baumannii* infections. However, further studies are needed to assess if minocycline monotherapy is sufficient or whether it should be utilized as part of a combination therapy. Further studies determining the clinical relevance of these results are warranted. Molecular studies are suggested to be conducted on epidemiology of *A. baumannii* with emphasis on drug resistance especially for colistin. Antibiotic stewardship should be implemented as it acts as an effective strategy to control antibiotic resistance in healthcare settings.

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IN VITRO ACTIVITY OF COLISTIN IN COMBINATION WITH DORIPENEM AGAINST CARBAPENEM NON-SUSCEPTIBLE *ACINETOBACTER BAUMANNII*

Key words: Carbapenem, resistant, *A. baumannii*, synergistic combinations, Agar dilution, E-test.

In this study we tested the *in vitro* activity of colistin in combination with doripenem against carbapenem non-susceptible *A. baumannii* isolates.

Our study findings showed that colistin is frequently synergistic with doripenem *in vitro* against carbapenem non-susceptible *A. baumannii* isolates.

Ռեհամ Մագդի Վասֆի, Նեվին Սոբհի Ֆամ, Մուստաֆա Քամել Սուլթան,
Ռագդա Հաֆեզ, Դոա Գամալ

IN VITRO ՊԱՅՄԱՆՆԵՐՈՒՄ ԴՈՐԻՊԵՆԵՄԻ ՀԵՏ ԶՈՒԳԱԿՑՎԱԾ ԿՈԼԻՍՏԻՆԻ ԱԶԴԵՑՈՒԹՅՈՒՆԸ *A. BAUMANNII*-Ի ԿԱՐԲԱՊԵՆԵՄ ՈՉ ԶԳԱՅՈՒՆ ՇՏԱՄԻ ՆԿԱՏՄԱՄԲ

Բանալի բառեր՝ կարբապենեմներ, դիմադրիչ, *A. baumannii*, սիներգետիկ խառնուրդ, ագար-ագարի լուծում, է-թեստ:

Սույն աշխատանքի նպատակն է *in vitro* պայմաններում ուսումնասիրել A. baumannii-ի կարբապենեմ ոչ զգայուն շտամի նկատմամբ դորիպենեմի հետ զուգակցված կոլիստինի ազդեցությունը:

Հեղինակներին հաջողվել է ցույց տալ, որ *in vitro* պայմաններում կոլիստինը հաճախ սիներգիստ է գործում դորիպենեմի հետ *A. baumannii*-ի կարբապենեմ ոչ զգայուն շտամների նկատմամբ:

Рехам Магди Васфи, Невин Собхи Фам, Мустафа Камел Султан,
Рагда Хафез, Доа Гамал

ВЛИЯНИЕ КОЛИСТИНА В СОЧЕТАНИИ С ДОРИПЕМЕНОМ В УСЛОВИЯХ *IN VITRO* ПО ОТНОШЕНИЮ К НЕЧУВСТВИТЕЛЬНОМУ К КАРБАПЕНЕМУ ШТАММУ *A. BAUMANNII*

Ключевые слова: карбапенемы, устойчивый, *A. Baumannii*, синергетическая смесь, растворимость агар-агара, э-тест.

Целью данной работы является рассмотрение влияние колистина в сочетании с дорипеменом в условиях *in vitro* по отношению к нечувствительному к карбапенему штамму *A. baumannii*.

Авторам статьи удалось показать, что во время взаимодействия в условиях *in vitro* колистин часто образует синергитические смеси с дорипенемом по отношению к нечувствительному к карбапенему штамму *A. baumannii*.