Antimicrobial susceptibility patterns of multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* against carbapenems, colistin, and tigecycline

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ABSTRACT

الأهداف: اختبار حساسية الزائفة الزنجارية والعصيات الراكدة للكاربابينيمات جنباً إلى جنب مع كوليستين وتيجيليسيكلين كخيارات علاجية بديلة.

الطريقة: أُجريت هذه الدراسة في مستشفى الملك خالد الجامعي، الرياض، المملكة العربية السعودية وذلك خلال الفترة من يونيو إلى ديسمبر 2010م. شملت الدراسة ما مجموعة 117 عزلة من البكتريا ذات المقاومة المتعددة للمضادات الحيوية (MDR) من مرضى المستشفى. ولقد كان منها 84 عزلة من بكتيريا العصيات الراكدة و33 عزلة من بكتيريا الزائفة الزنجارية. كما أنه قد تم تحديدها باستخدام جهاز المايكروسكان وكاواى 96 بلص. وتم تحديد الحد الأدنى للتركيز المثبط باستخدام اختبار إي وفقاً للنقاط الحاسمة لمعهد المعايير السريرية والمعملية (CLSI).

النتائج: لقد كانت الأغلبية من سلالات العصيات الراكدة مقاومة للأميبينيم (90.5%)، تليها المقاومة ضد كل من مضاد ميروبينيم (90.5%)، ودوريبينيم (77.4%). في حين كانت نسبة المقاومة أعلى في حالة الزائفة الزنجارية ضد كلا من مضاد أمبينيم (90.9%)، ومضاد ميروبينيم (81.8%). بينما كانت نسبة المقاومة 39.4% ضد مضاد دوربينيم. وقد أظهر مضاد كوليستين نشاطاً ممتازاً ضد العصيات الراكدة (100%)، والزائفة الزنجارية (93.9%)، بينما كان 89.3% من سلالات العصيات الراكدة حساسة لمضاد تيجيليسيكلين.

خاتمة: لقد وُجد بأن من بين مجموعة كاربابينيمات فقد كان مضاد دوربينيم هو الأقوى ضد بكتيريا الزائفة الزنجارية، في حين ثبتت فعالية كوليستين كخيار علاجي بديل ضد العصيات الراكدة أو الزائفة الزنجارية. بينما يبقى مضاد تيجيليسكلين الخيار الأفضل لعلاج العصيات الراكدة ذات المقاومة المتعددة للمضادات الحيوية.

Objectives: To examine susceptibility of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter baumannii* (*A. baumannii*) against carbapenems along with colistin and tigecycline as alternative therapeutic options.

Methods: A total of 117 strains of multidrug-resistant (MDR) non-fermenting Gram negative bacteria isolated from non-duplicate samples were collected consecutively. We included one sample from each patient (84 isolates of *A. baumannii* and 33 isolates of *P. aeruginosa* isolated from patients seen at King Khalid University Hospital, Riyadh, Saudi Arabia, from June to December 2010). Isolates were identified by the MicroScan WalkAway 96 Plus system. The minimum inhibitory concentrations (MICs) were determined by E-test following the Clinical and Laboratory Standards Institute breakpoint recommendations.

Results: Most *A. baumannii* strains were resistant to imipenem (90.5%), meropenem (90.5%), and doripenem (77.4%). Whereas, a higher percentage of *P. aeruginosa* was resistant to imipenem (90.9%), and meropenem (81.8%), only 39.4% were resistant to doripenem. Colistin had excellent activity against both *A. baumannii* (100%) and *P. aeruginosa* (93.9%), while 89.3% of *A. baumannii* strains were susceptible to tigecycline.

Conclusion: Among the carbapenems, doripenem was found to be the most potent antimicrobial agent against *P. aeruginosa,* whereas colistin proved to be an effective alternative antimicrobial agent for treatment of *A. baumannii* or *P. aeruginosa*. Tigecycline remains the best therapeutic option for MDR *A. baumannii*.

Saudi Med J 2012; Vol. 33 (7): 750-755

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Received 5th March 2012. Accepted 17th June 2012.

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The widespread and indiscriminate use of antibiotics are the key factors influencing the prevalence and distribution of drug resistance in any community or nosocomial setting.[1,2] Infections due to multidrug-resistant organisms (MDROs) especially Gram negative non-fermenting bacteria like *Acinetobacter baumannii* (*A. baumannii*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) are increasing, ultimately leading to shortage of clinically effective antibiotics. Multidrug-resistant (MDR) bacteria are defined as resistant to one or more classes of antibiotics.[3] *Acinetobacter baumannii* and *P. aeruginosa* are important nosocomial pathogens and are often resistant to almost all beta-lactam antibiotics, aminoglycosides, and quinolones.[2] Emergence and spread of carbapenem resistant and metallo beta-lactamase producing *P. aeruginosa* and *A. baumannii*, has further challenged the efficacy of antimicrobial therapy. Increasing resistance against commonly used antibiotics limits the therapeutic options emphasizing the need for alternative antibiotics.

Colistin is a polypeptide antibiotic that has been used rarely due to concerns about its efficacy and safety. In recent years, the drug has reemerged as an alternative for the management of MDR Gram negative bacterial infections.[4-7] *In vitro*, colistin exhibits an excellent activity against a variety of Gram-negative bacilli, and *in vivo*, has not shown a serious toxicity after prolonged intravenous administration.[8] *Pseudomonas aeruginosa* and *A. baumannii* are among the main pathogens targeted by colistin and the Clinical and Laboratory Standards Institute (CLSI) have published MIC interpretation guidelines only for these organisms.[9]

Along with colistin and tigecycline a new semi-synthetic glycylcycline approved by the Food and Drug Administration (FDA) in June 2005 appears to be a very potent agent *in vitro* against *A. baumannii*.[10] This drug has an extended spectrum of activities against susceptible and MDR Gram-positive and negative organisms, anaerobes, and atypical pathogens but has also been associated with an increase risk of mortality from Gram positive infections.[11] Sufficient clinical experience with tigecycline is lacking, and the FDA has approved its use only for complicated intra abdominal and complicated skin infections.[12,13] *Pseudomonas aeruginosa* are intrinsically resistant to tigecycline due to RND-type efflux pumps and tigecycline should not be tested or reported in the clinical laboratory.[14] Doripenem is a novel, broad-spectrum parenteral carbapenem and has been shown to have better activity than other antibiotics from the same class.[15]

Because of the well-documented regional variations in the susceptibility patterns of microbes this study was performed to investigate the antimicrobial susceptibility patterns of MDR *A. baumannii* and *P. aeruginosa* against colistin, tigecycline, and doripenem as alternatives for the management of MDR Gram negative bacterial infections at King Khalid University Hospital (KKUH).

Methods. A total of 117 strains of MDR non-fermenting Gram negative bacteria isolated from non-duplicate samples were collected consecutively. We included one sample from each patient (84 isolates of *A. baumannii* and 33 isolates of *P. aeruginosa* isolated from patients seen at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, from June to December 2010). Among all Gram negative non-fermenting bacteria, *P. aeruginosa* and *A. baumannii* are the most commonly isolated organisms in our institution with high rates of resistance to the routinely used empirical antibiotics like beta-lactam antibiotics, fluoroquinolones, and aminoglycosides. These strains were isolated from a variety of body sites including wounds, respiratory, urine, swabs, tissues, blood, and other sterile body sites. **Table 1** shows various body sites and locations of patients at the time of sample collection. The bacterial identifications were performed by routine laboratory methods in the microbiology laboratory of KKUH using MicroScan WalkAway 96 Plus system (Siemens Healthcare Diagnostic Inc, New York, USA).

This study was approved by the Ethical Committee at KKUH.

The minimum inhibitory concentrations (MIC) determination. Minimum inhibitory concentrations were determined by the E-test (AB Biodisk, Solna, Sweden). The MIC was interpreted as the value at which the inhibition zone intercepted the scale on the E-test strip. The E-test method was applied according to the manufacturer's instructions. Bacterial suspensions were first adjusted to a turbidity equivalent to 0.5 McFarland standard using a calibrated turbidimeter as recommended by the CLSI.[16] Mueller-Hinton agar (Oxoid, Basingstoke, UK) was used for susceptibility testing and all test media were incubated at 35°C in normal atmosphere for 20-24 hours. The susceptibility test results were interpreted according to CLSI breakpoint recommendations.[16] Tigecycline breakpoints

Disclosure. This study was funded by the King Saud University-Yale University partnership in Global Health.

are not available from CLSI for *P. aeruginosa* and *A. baumannii*. These results were interpreted according to breakpoints reported in the literature as ≤2, 4, and ≥8 mg/L for susceptible, intermediate, and resistant strains, respectively. *Escherichia coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) were used as quality control strains for antibiotic susceptibility testing.

Statistical analysis. All related statistical analysis were performed using SPSS 12.0 statistical software (SPSS Inc. Wacker Drive, Chicago, IL USA).

Results. The lower respiratory tract was the main source of the samples that contained MDR *A. baumannii* and *P. aeruginosa* (59 [50.4%]), while wound samples were the second most common site (34 [29%]). A relatively small numbers of strains were isolated from sterile body sites, urine, and superficial swabs (**Table 1**). Most of the MDR *A. baumannii* and *P. aeruginosa* strains were isolated from samples collected from intensive care units (62 [53%]) followed by (48 [41%]) hospitalized patients in other units and only a few samples were received from oncology or primary care clinics (**Table 2**).

Comparing the 2 organisms, *A. baumannii* was isolated in a higher number 84 (71.8%) than *P. aeruginosa*, which was present in 33 (28.2%) specimens. **Table 3** describes the antimicrobial activity of 3 carbapenems, colistin, and tigecycline against *A. baumannii* and *P. aeruginosa* along with the MIC range using E-test. Of the total 84 isolates of *A. baumannii* a vast majority were resistant to imipenem 76 (90.5%), meropenem 76 (90.5%), and doripenem 65 (77.4%). Whereas none of the *A. baumannii* isolates was resistant to colistin, only 9 (10.7%) were found to be resistant to tigecycline. Among the 33 isolates of *P. aeruginosa,* a higher percentage of resistance against imipenem 30 (90.9%) and meropenem 27 (81.8%) was observed compared to doripenem which was 13 (39.4%). No *A. baumannii* was resistant to colistin. Two (6.1%) *P. aeruginosa* isolates were found to be resistant to colistin. Similarly, a small percentage of *A. baumannii* isolates (9 [10.7%]) were found to be resistant to tigecycline; 28 (84.9%) of *P. aeruginosa* isolates resisted the bactericidal activity of tigecycline. **Figures 1 & 2** show the cumulative MICs distribution curves of carbapenems against *A. baumannii* and *P. aeruginosa* strains and demonstrate the left shift toward the lower MICs of doripenem curve for both *A. baumannii* and *P. aeruginosa* strains compared with other carbapenems. **Figure 3** shows a shift to the left for the cumulative MICs distribution

Table 1 - Types of samples collected from 117 patients included in the study at King Khalid University Hospital, Riyadh, Saudi Arabia.

Sample source	N	(%)	*A. baumannii* n	(%)	*P. aeruginosa* n	(%)
Blood/sterile body fluids and tissue	3	(2.6)	3	(3.6)	0	(0)
Wounds	34	(29.0)	24	(29.6)	10	(30.3)
*Respiratory	59	(50.4)	42	(50.0)	17	(51.5)
Urine	12	(10.3)	8	(9.5)	4	(12.1)
Superficial swabs and catheter tips	9	(7.7)	7	(8.3)	2	(6.1)
Total	**117**	**(100)**	**84**	**(100.0)**	**33**	**(100)**

*Respiratory samples - include sputum, bronchoalveolar lavage (BAL) and tracheal aspirates.
A. baumannii - Acinetobacter baumannii, P. aeruginosa - Pseudomonas aeruginosa

Table 2 - Different hospital locations for collection of positive samples for multidrug-resistant organisms from 117 patients.

Location	Total N	(%)	*A. baumannii* n	(%)	*P. aeruginosa* n	(%)
ICUs	**62**	**(53.0)**	50	(59.5)	12	(36.4)
Hospital units other than ICUs	**48**	**(41.0)**	30	(35.7)	18	(54.5)
Primary care clinics	**3**	**(2.6)**	2	(2.4)	1	(3.0)
Oncology	**4**	**(3.4)**	2	(2.4)	2	(6.1)
Total	**117**	**(100)**	84	(100)	33	(100)

ICUs - intensive care units including surgical, medical, neonatal and pediatrics intensive care units. *A. baumannii - Acinetobacter baumannii, P. aeruginosa - Pseudomonas aeruginosa*

Table 3 - Antimicrobial activity of imipenem, meropenem, doripenem, colistin and tigecycline against 117 isolates.

Species (Total number tested)	Drugs	Range	Susceptible n	Susceptible (%)	Resistant n	Resistant (%)
A. baumannii (n=84)	Imipenem	0.25 - >32.0	8	(9.5)	76	(90.5)
	Meropenem	0.25 - >32.0	8	(9.5)	76	(90.5)
	Doripenem	0.25 - >32.0	19	(22.6)	65	(77.5)
	Colistin	0.004 - 1.25	84	(100.0)	0	(0%)
	Tigecycline	0.047 - 16.0	75	(89.3)	9	(10.7)
P. aeruginosa (n=33)	Imipenem	2.0 - >32.0	3	(9.1)	30	(90.9)
	Meropenem	0.125 - >32.0	6	(18.2)	27	(81.8)
	Doripenem	0.125 - >32.0	20	(60.6)	13	(39.4)
	Colistin	0.125 - 3.0	31	(93.9)	2	(6.1)
	Tigecycline	1.0 - 24.0	5	(15.2)	28	(84.9)

A. baumannii - Acinetobacter baumannii, P. aeruginosa - Pseudomonas aeruginosa

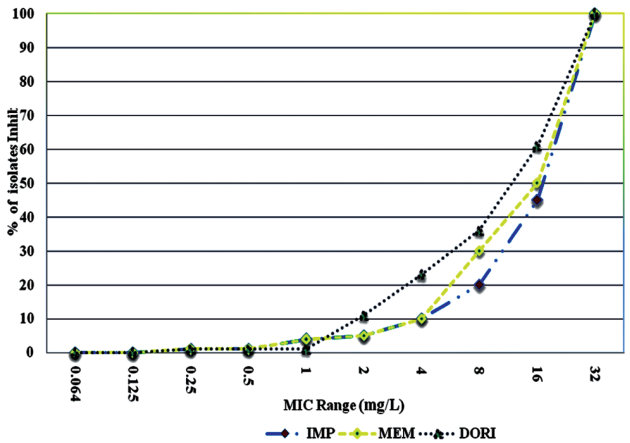

Figure 1 - Comparative activity of 3 carbapenems against *Acinetobacter baumannii* (n=84). Cumulative curve of doripenem MICs (black dotted line) showing slight shift towards the left indicating lower MICs of doripenem against *Acinetobacter baumannii* as compared to other carbapenems. MIC - minimal inhibitory concentration, IMP - imipenem, MEM - meropenem, DORI - doripenem, inhib - Inhibition.

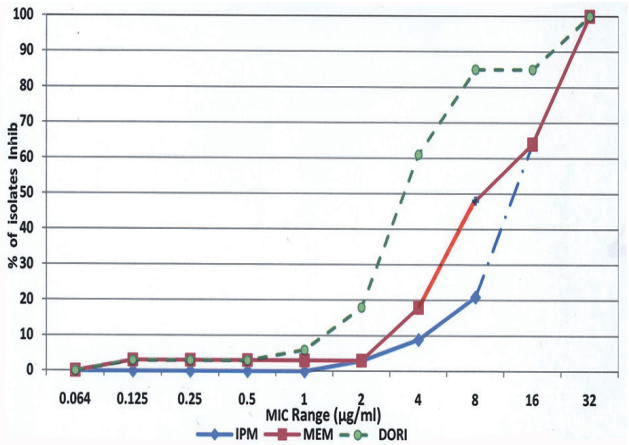

Figure 2 - Comparative activity of 3 carbapenems against *Pseudomonas aeruginosa (P. aeruginosa)* (n=33). Cumulative curves comparing to the doripenem MICs of *P. aeruginosa* (green dotted line) shifted to the left compared with MIC curves of imipenem and meropenem. MIC - minimal inhibitory concentration, IPM - imipenem, MEM - meropenem, DORI - doripenem

curve of colistin against *A. baumannii* strains compared with *P. aeruginosa*. A shift to the right was evident in the cumulative MICs distribution curve of tigecycline against *A. baumannii*.

Discussion. This study describes susceptibility patterns of MDR *A. baumannii* and *P. aeruginosa* against carbapenems, colistin and tigecycline. These microorganisms were the most frequent MDR non-fermenting Gram negative strains isolated from various clinical specimens evaluated in the present study. The non-fermenters, *A. baumannii* and *P. aeruginosa* have emerged as important nosocomial pathogens, causing opportunistic infections in immunocompromised hosts.[17] Multidrug resistance, defined as carbapenem resistance or resistance to 3 classes of antimicrobials is increasing amongst these organisms making it difficult to choose appropriate empiric antimicrobial therapy.[18] In the present study, both *A. baumannii* and *P. aeruginosa* strains were frequently resistant to imipenem, meropenem, and doripenem. Among the 3 carbapenems tested, resistance against doripenem was the least, 77.4% for *A. baumannii* and 39.4% for *P. aeruginosa*, but this is less than the ideal considering the empiric therapy for serious bacterial infections.

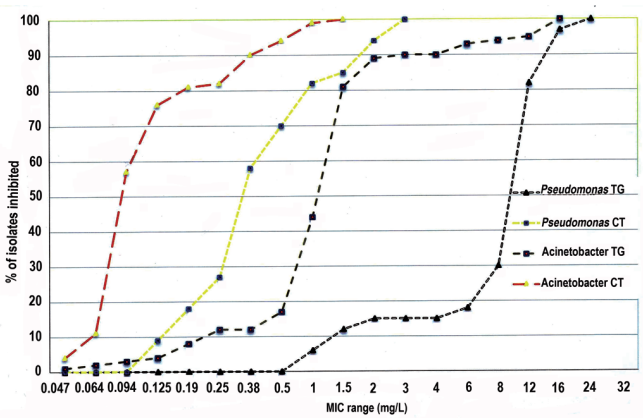

Figure 3 - Comparative activity of colistin and tigecycline against *Acinetobacter baumannii (A. baumannii)* (n=84) and *Pseudomonas aeruginosa (P. aeruginosa)* (n=33). Minimal inhibitory concentrations (MICs) cumulative curve for colistin (red dotted line) shows a shift to the left against *A. baumannii* followed by the colistin MICs cumulative curve against *P. aeruginosa* (yellow dotted line) and tigecycline MIC cumulative curve against *A. baumannii* (black dotted line with squares). Tigecycline MIC cumulative curve against *P. aeruginosa* is located at the right side of the graph MIC - minimal inhibitory concentration, TG - tigecycline, CT - colistin

Bogiel et al[19] reported 39% of *Pseudomonas spps*, as resistant to doripenem; however, resistance against *Acinetobacter spp* was 28.4%.[19] Increased use of carbapenems to treat infection of third generation cephalosporin-resistant Gram-negative bacilli resulted in emergence of carbapenem-resistant *P. aeruginosa* and *Acinetobacter spp*. In a Korean surveillance study, during 1997 to 2009, imipenem-resistant *P. aeruginosa* and *Acinetobacter spp* increased from 17-26% and 1-51%, respectively.[20]

The increasing resistance in *A. baumannii* and *P. aeruginosa* against carbapenems is worrisome. Colistin is an antibiotic in which there has had a revived interest recently for treating infections caused by MDR *A. baumannii* and *P. aeruginosa*. In critically ill patients, colistin is increasingly used as salvage therapy.[21] Our *in vitro* study showed that all the *A. baumannii* strains were susceptible to colistin. Colistin resistant *Acinetobacter spp* strains have been rarely reported in the literature. In a study, none of the 139 imipenem resistant *A. baumannii* isolates recovered from 4 hospitals in 2006 showed resistance to colistin. Sheng et al,[22] reported 3% colistin resistance among *A. baumannii* (n=12). In our study 6% *P. aeruginosa* strains were resistant to colistin in accordance with a CLSI breakpoint of ≤2 mg/L as the susceptible breakpoint and >2 mg/L as the resistant breakpoint. Following other guidelines using different breakpoints such as set by the British Society for Antimicrobial Chemotherapy (BSAC; ≤4mg/ L as susceptible and ≥8 mg/L as resistant)[7] the percentage of resistant strains of *A. baumannii* and *P. aeruginosa* may vary.

Although the novel agent tigecycline has a significant activity against MDR *A. baumannii*, it is not active against *P. aeruginosa* due to the efflux mechanism by MexXY-OprM.[23] Tigecycline represents a new treatment choice for MDROs like *A. baumannii*, but the increasing resistance of *A. baumannii* to tigecycline (10.7%) is an indicator to use this drug wisely in selected cases and preferably in combination therapy. The FDA has issued a warning regarding increased mortality risk associated with tigecycline based on a pooled analysis of 13 clinical trials.[24] Henwood et al[25] reported 9% non susceptibility among the tested (n=443) *A. baumannii* strains. In another study from Turkey, Akinci et al,[26] reported 19.4% of Acinetobacter strains as non susceptible to tigecycline.[26] Al-Sweih et al[27] reported 13.6% and 12% resistance to tigecycline and colistin, respectively (n=250).[27] However, in our study not a single *A. baumannii* strain was found to be resistant to colistin. All tigecycline non susceptible *A. baumannii* strains (10.72%) were sensitive to colistin with an MIC range of 0.25-0.38 mg/l.

The use of colistin and tigecycline must be restrictive and discriminative so as to hamper the emergence of resistant clones. Our study also highlights the need for time to time evaluation of the susceptibility patterns of MDROs in hospital setups to help formulate the antibiotic policies. For isolates from Saudi Arabia, tigecycline remains a therapeutic option for MDR *A. baumannii,* and colistin is an important alternative treatment option against both *A. baumannii* and *P. aeruginosa* and may be considered as empiric therapy in cases of serious infections when these organisms are suspected and hospital wide resistant rates are high.

The limitations of this study were the short duration and lack of clinical information particularly on the exposure to antibiotics. Our future plan is to extend the period to at least one year in addition to extensive review of the patients clinical information to identify the risk factors that predispose these patients to infections due to MDROs.

In conclusion, doripenem was found to be the most potent antimicrobial against *A. baumannii* and *P. aeruginosa* among all the carbapenems tested. Whereas colistin proved to be a highly active antimicrobial agent against *A. baumannii* and *P. aeruginosa,* tigecycline remains an alternative antimicrobial agent for MDR *A. baumannii*.

Acknowledgment. *We would like to thank all the technical staff at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, for their work in identifying the isolates as per standard guidelines and for their help in data collection and analysis.*

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