MIC and Synergy Testing Guide Antimicrobial Treatment of Ventilator-Associated Pneumonia due to Carbapenem-Resistant *Acinetobacter baumannii*

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Background: *The studies regarding the use of information from in vitro study to guide antimicrobial combination therapy in clinical settings are limited.*
Objective: *To determine feasibility and impact of the application of MIC and synergy testing to guide antimicrobial therapy in clinical setting.*
Material and Method: *Patients with ventilator-associated pneumonia (VAP) due to carbapenem-resistant A. baumannii (CRAB) infections were enrolled. Susceptibility information obtained from disk diffusion, MIC determination, and synergy testing with E-test method was used to select antimicrobial agent to combine with colistin. Treatment outcomes were assessed following antimicrobial treatment.*
Results: *Ten VAP-patients with CRAB infections were enrolled. Seven patients received non-active CRAB regimen as empirical therapy. The results from disk diffusion, MIC determination, and synergy testing enabled the clinicians to choose regimen with potential to be successful in 70%, 30%, and 20%, respectively. Finally, nine patients received colistin-sulbactam and one patient received colistin-imipenem. Favorable clinical and microbiological outcomes were observed in nine and six out of 10 patients, respectively.*
Conclusion: *The information from MIC determination and synergy testing by E-test method enables optimization of treatment regimens for VAP-patients with CRAB infections. This strategy revealed favorable treatment outcomes and that it is feasible to perform in clinical setting.*

Keywords: *Acinetobacter baumannii, CRAB, MIC determination, Synergy testing, Combination therapy, Colistin, Carbapenems, Sulbactam*

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Acinetobacter baumannii is a common cause of nosocomial and ventilator-associated pneumonia (VAP) in Thailand[1-3]. At present, there is limited antimicrobial therapy for multi-drug resistant (MDR) *A. baumannii*, especially carbapenem-resistant *A. baumannii* (CRAB). Consequently, patients infected with this microorganism often received inactive or partially active empirical drug regimens[3,4]. Combination antimicrobial therapy has been proposed as an option for treating CRAB infections since it improves treatment outcomes and prevents the emergence of drug resistance[5-7]. Based on the data from in vitro synergy and retrospective studies, colistin (CST)-carbapenems and CST-sulbactam (SUL) combinations are commonly selected to treat CRAB infections[8-11]. In Thailand, CST is the recommended primary agent in combination therapy for CRAB since the majority of isolates are susceptible to the compound[2,4,12]. The second agent administered in combination with CST is selected based on bacterial susceptibility testing. In routine practice, antibiogram data of each institution are reviewed to select the second

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agent for empirical therapy. Therefore, when the susceptibility test result is reported the antimicobial agents will be modified accordingly. If CRAB is susceptible to SUL, then SUL is administered instead of carbapenems. If CRAB is resistant to both secondary antimicrobials, MIC and synergy testing are performed in the attempt to improve therapy. However, this strategy is seldom applied in clinical practice. Therefore, we conducted a prospective pilot study to determine the feasibility and the treatment outcomes of using MIC determination and synergy testing to optimize the treatment regimen of patients with VAP associated with CRAB infection.

Material and Method

This prospective study was performed at Songklanagarind Hospital, a tertiary care university hospital located in Hat Yai, Thailand. The study was approved by the Ethics Committee of Songklanagarind Hospital and informed consent was obtained from all participants or their legal representatives. Consecutive patients of 18 years of age or older who developed VAP due to CRAB infection were enrolled between January and June 2014. VAP was defined according to the criteria of the American Thoracic Society; the Infectious Diseases Society of America (ATS/IDSA)[13]. Patients who were allergic to CST, imipenem (IPM), meropenem (MEM) or cefoperazone/sulbactam (SUL), or those having an Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 30 were excluded.

Based on the results of in vitro data, the antimicrobial regimen for each CRAB-infected patient was considered in two stages. Stage 1, from routinely disk diffusion test, if CRAB isolate was susceptible (S) or intermediate (I) to SUL, the combination of CST-SUL would be considered for the treatment of VAP. Alternatively, if the CRAB isolate was resistant (R) to SUL, a combination of CST-SUL or CST-carbapenems would be considered. Stage 2, MIC determination and synergy study with E-test method were performed to determine the MIC and fractional inhibitory concentration index (ΣFIC) of each CRAB isolate[14]. The antimicrobials (SUL, IMP, or MEM) that displayed the best MIC and ΣFIC profile were considered for combining with CST for treatment of VAP. MIC determination and synergy testing were carried out as soon as possible after enrollment of patients in the study.

The MIC values of CST, IPM, MEM, and SUL were determined using E-test strips (Biomerieux®). The E-test synergy study was carried out for CST-IPM, CST-MEM and CST-SUL combination. E-test strips were placed on the inoculums streaked MHA in a cross formation with 90° angle at the intersection between the scales at their respective MICs for the organism. The diameter of the zones of inhibition were measured and subsequently used to determine the MICs for ΣFIC calculation. The ΣFIC is calculated by comparing the value of the MIC of each agent alone with the MIC of that drug in combination. Fractional inhibitory concentration index was interpreted as follows: synergism at less than 0.5; additive between 0.5 and 1.0; indifferent between greater than 1.0 and 4.0; and antagonism at greater than 4.0[14-16]. The Clinical & Laboratory Standards Institute (CLSI) breakpoints 2013 were used to determine susceptibilities to CST and carbapenems[17]. SUL susceptibility was interpreted based on criteria from previous study[18].

The following antibiotic regimens were established for patients enrolled in the present study: IPM (Tienam®, MSD) 4 gm/day, MEM (Meronem®, AstraZeneca) 6 gm/day, and SUL (Cebactam®, LBS. Laboratory) 8 gm/day (4 gram/day of SUL). Individual doses of carbapenems and SUL were administrated by prolonged intravenous infusion (4-hour) and the dose was adjusted according to creatinine clearance estimated by the Cockcroft-Gault Equation[19,20]. The dose of CST (Colistate 150®, Atlantic Laboratories) was adjusted according to the previous study[21].

The clinical response and overall mortality were evaluated at day-14 and day-28 after VAP diagnosis. The clinical responses were defined as follows; (1) complete response: resolution of fever or hypothermia, absence of purulent in the endotracheal aspirate (EA), the ratio of partial pressure of arterial O_2 to the fraction of inspired O_2 (PaO_2/FiO_2 ratio) more than 240 mmHg or mechanical ventilation no longer needed, and white blood cell (WBC) in the 4,000 to 12,000 cell/μL range; (2) partial response: the patient did not fulfill all the requirements pertaining to complete response; and (3) failure: persistence or worsening of all symptoms and signs of infection.

The microbiological response at the end of treatment was classified as favorable outcome (eradication, presumed eradication), persistence of infection and super-infection. *Eradication* was defined if there was no *A. baumannii* in EA culture. Presumed eradication was the absence of results on EA culture because the patient was classified as a clinical success and was unable to produce sputum. Persistence was defined if the *A. baumannii* was present in EA culture.

The outcome was classified as super-infection if new pathogens/causative organisms were discovered in sputum samples and were judged to cause VAP. The time to microbiological clearance was defined as the time interval between the initiation of CST-based combination therapy and the first negative EA culture.

Results

During the study period, VAP-patients infected with CRAB were enrolled. The demographics and clinical characteristics of the ten VAP-patients infected with CRAB enrolled in the present study were summarized in Table 1. The results of susceptibility testing, MIC determination and synergy testing were shown in Table 2. From routine disk diffusion method, SUL susceptibility was graded to be S, I, and R in 3, 4, and 3 isolates. However, SUL susceptibility was S, I and R in 3, 5 and 2 strains when interpreted from E-test MIC of each CRAB isolate. The discrepancy between

Table 1. Demographics, clinical characteristics of the enrolled patients

Variables	n = 10
Male	6 (60%)
Age in year ± SD (range)	60±19.6 (22 to 78)
Weight in kilogram ± SD (range)	57.4±10.8 (40 to 70)
Creatinine clearance (mL/min)	
>90	3
61 to 90	3
<15 (intermittent hemodialysis)	4 (3)
APACHE II score ± SD (range)	15.1±5.5 (7 to 27)
CPIS score ± SD (range)	7±0.67 (6 to 8)
SOFA score ± SD (range)	6.8±3.5 (5 to 13)
Co-morbidities	
Cardiovascular diseases	3
Cerebrovascular diseases	2
Malignancy	2
Chronic obstructive pulmonary disease	2
Chronic kidney disease	1
Cirrhosis	1
Nephrotic syndrome	1
Peripheral artery disease	1
Trauma	1

APACHE = Acute Physiology and Chronic Health Evaluation; CPIS = Clinical Pulmonary Infection Score; SOFA = Sequential Organ Failure Assessment

Table 2. Susceptibility test, MIC determination and synergy studies with E-test method of 10 CRAB isolates

No.	The interpretation of SUL susceptibility		MIC (mg/L)				MICs when combined testing with CST (mg/L) (ΣFIC: interpretation)		
	Disk diffusion	E-test	SUL	IPM	MEM	CST	SUL/CST	IPM/CST	MEM/CST
1	I	R	32	16	16	0.19	12/0.06 (0.7:ADD)	16/0.19 (2.0:IND)	16/0.19(2.0:IND)
2	S	I	6	>32	16	0.09	6/0.09(2.0:IND)	32/0.09 (ND)	16/0.09 (2.0:IND)
3	S	S	2	>32	16	0.38	1.5/0.13 (1.1:IND)	16/0.125(ND)	8/0.13 (0.8:ADD)
4	I	I	8	32	32	2.00	3/0.13 (0.4:SYN)	12/0.13 (0.4:SYN)	16/0.25 (0.6:ADD)
5	S	S	2	32	16	0.19	2/0.19 (2.0:IND)	24/0.19(1.8:IND)	24/0.190(2.5:IND)
6	R	I	12	>32	32	0.19	8/0.13 (1.3:IND)	24/0.13 (ND)	24/0.13(1.4:IND)
7	R	I	8	32	32	0.13	8/0.25 (3.0:IND)	24/0.13 (1.8:IND)	24/0.13 (1.8:IND)
8	I	I	8	>32	>32	0.25	6/0.19 (1.5:IND)	32/0.13 (ND)	32/0.13 (ND)
9	I	S	4	24	16	0.13	2/0.09 (1.3:IND)	16/0.09(1.4:IND)	12/0.09(1.5:IND)
10	R	R	16	>32	32	0.13	12/0.13 (1.8:IND)	24/0.13 (ND)	32/0.13 (2.0:IND)

ADD = additive; CST = colistin; ΣFIC = fractional inhibitory concentration index; IND = indifferent; IPM = imipenem; MEM = meropenem; ND = non-determined; SUL = sulbactam; SYN = synergistic

disk diffusion and E-test method were detected as discrepancy in half of isolates. The MICs of SUL, CST, IPM, and MEM against CRAB were 2 to 32, 0.094 to 2.0, 16 to greater than 32, and 16 to greater than 32 mg/L, respectively. Synergy testing revealed a reduction in the MICs of SUL, IPM, MEM, and CST against CRAB. However, only the results for one isolate (No. 4) demonstrated synergism of CST-SUL and CST-IPM. Tests on five isolates (No. 2, 3, 6, 8, and 10) and one isolate (No. 8) results in MICs for IPM and MEM exceeded the highest concentration on E-test strip; therefore, synergy rate of carbapenems and CST combination could not be confirmed.

Monotherapy and combination therapy regimens were ordered as empirical treatment regimens in seven and three patients, respectively (Table 3). The drug susceptibility of CRABs measured using the disk diffusion method revealed the monotherapy regimens were ineffective and were consequently changed to combination regimens. Analysis of the results of the disk diffusion method (Stage 1), initially led to selection of a combination of CST-SUL for seven out of 10 patients. Two patients who were infected with a SUL-resistant strain (No. 6, 10) received CST-IPM combination therapy. One patient (No. 1) although being infected with CRAB classified as intermediate SUL susceptibility, also received CST-IPM combination therapy to cover *P. aeruginosa* septic arthritis.

Based on the results of MIC determination and synergy studies (Stage 2), the antimicrobial treatment regimen of patients No. 6 and 10 was subsequently changed from CST-IPM to CST-SUL. Although the CST-SUL MIC and ΣFIC for patient No. 1 showed better profiles compared with CST-carbapenems, the patient received CST-IPM throughout treatment. Finally, nine patients received CST-SUL combination therapy and one patient received CST-IPM combination therapy. The mean (±SD) duration of treatment was 14.4±1.9 days. Time to complete the MIC determination and synergy test was 3±0.8 days from enrollment.

At the end of the treatment, complete clinical response and partial response were observed in nine patients (Table 3). Treatment failure was concluded in one patient. Favorable microbiological outcomes were observed in six patients consisting of five eradications and one presumed eradication. *A. baumannii* persistently grew in quantitative EA culture until the end of treatment in three patients. However, there was no recurrent episode of CRAB infected pneumonia in these patients. One patient (No. 9) had *P. aeruginosa* super-infection that consequently resulted in treatment failure. The mean time to microbiological clearance among six patients who had favorable microbiological outcomes was 4.5±2.4 days. Two patients (No. 5, 9) died from subdural hematoma and acute respiratory distress syndrome (ARDS), respectively.

Discussion

Despite *A. baumannii* being a low-virulent

Table 3. Antimicrobial regimen and treatment outcomes at the end of treatment

Patient No.	Empirical regimen	Stage 1 regimen	Stage 2 regimen	Clinical response	Microbiological response
1	IPM/CST	IPM/CST	IPM/CST	PAR	PER
2	IPM/CST	SUL/CST	SUL/CST	COM	PER
3	CRO	SUL/CST	SUL/CST	PAR	ERA
4	TZP	SUL/CST	SUL/CST	COM	ERA
5	IPM	SUL/CST	SUL/CST	PAR	ERA
6	TZP	IPM/CST	SUL/CST	COM	PER
7	MEM	SUL/CST	SUL/CST	PAR	ERA
8	SUL/CST	SUL/CST	SUL/CST	COM	ERA
9	TZP	SUL/CST	SUL/CST	FAIL	SUPER
10	IPM	IPM/CST	SUL/CST	COM	PRE-ERA

Stage 1 = antimicrobial regimen based on the results from routinely disk diffusion test; Stage 2 = antimicrobial regimen based on the results from MIC determination and synergy studies with E-test method
COM = complete response; CRO = ceftriaxone; CST = colistin; ERA = eradication; FAIL = failure; I = intermediate; IPM = imipenem; MEM = meropenem; PAR = partial response; PER = persistent; PER-ERA = presumed eradication; R = resistance; S = susceptible; SUL = cefoperazone/sulbactam; SUPER = superinfection; TZP = piperacillin/tazobactam

pathogen, the mortality rate of CRAB infections is high because of the using non-coverage regimens[3,4]. There are two main strategies to improve clinical treatment outcome in patients infected with CRAB including: 1) applications of the pharmacokinetic-pharmacodynamic principles to optimize antimicrobial dosing regimens, and 2) combination antimicrobial therapy to enhance the probability of favorable treatment outcomes[3,4,22]. Antimicrobial synergy testing had been used to assess the interaction of antibiotic combinations in vitro, however there is not enough evidence to endorse in routine clinical use[16]. To our knowledge, the present study is the first prospective clinical study to determine the feasibility and impact of using MIC data and synergy studies to select regimen with potential to be successful for patients with VAP due to CRAB infections.

In the present study, in vitro information on antibacterial activity obtained from routine disk diffusion assay and E-tests were used to improve antimicrobial treatment regimen for individual CRAB-infected VAP patients. High dose and extended infusion of beta-lactam antimicrobial was applied to improve treatment outcome. The E-test was performed to determine the MIC and synergism of candidate antimicrobials since testing process is not labor intensive, it is easily performed, and completed in two to three days. Thus E-testing is feasible for obtaining MIC data and synergy estimations for selected drugs in the clinical setting.

In the present study, routine disk diffusion data were successfully used to guide the selection of antimicrobial treatment regimens for seven patients with CRABs were intermediate or susceptible to SUL. The MIC results were also used to select a potential successful treatment regimen for three patients (No. 6, 7, and 10) where *A. baumannii* resistant to both carbapenems and SUL. An additional synergy test was necessary to establish an effective treatment regimen for two patients (No. 1 and 10) where the MIC of carbapenems and SUL were high. We found a 50% discrepancy for SUL susceptibility of *A. baumannii* between disk diffusion and E-test measurement, which is higher than previously reported[18]. Although disk diffusion results could guide antimicrobial regimen in majority patients (70%), *A. baumannii* susceptibility testing of SUL based on disk diffusion must be interpreted with caution. It is recommended that the MIC of SUL should determine for all CRAB isolates in EA if SUL is the favored treatment option.

At the end of treatment, favorable clinical outcomes were obtained in nine of ten patients and favorable microbiological outcomes were obtained for six of the 10 patients. *A. baumannii* persistently grew in EA cultures from three patients (30%) who had good clinical outcomes, indicated colonization of CRAB. The clinical outcomes in our series agreed with previous studies of *A. baumannii*-associated VAP treatment that reported favorable clinical and microbiological outcomes between 34 and 67%, and 51 and 78%, respectively[7,10,23]. However, due to differences in study design, the method of evaluating microbiological outcomes, and definition of response rate, the results cannot directly comparable.

Several limitations may be identified in our study including the small number of patients. We did not compare the treatment outcomes of our intervention with the control group who received standard of care. The EAs that we used for VAP diagnosis and evaluation of microbiological outcomes are less specific for detecting the causal pathogens of VAP compared with bronchoalveolar lavage (BAL) and protected brush specimens (PBS). The present study investigated the effectiveness of CST-carbapenems and CST-SUL regimens for treating CRAB-associated VAP. The assessment of the effectiveness of alternative combination therapies based on candidate antimicrobials such as CST-tigecycline or CST-fosfomycin had not been evaluated.

In conclusion, MIC determination and synergy testing by E-test method are feasible to perform for individual VAP-patients with CRAB infections in the clinical setting. Consideration of combination antibacterial treatment regimens is recommended in clinical settings characterized by a high incidence of CRAB infection. The susceptibility data obtained from disk diffusion and MIC results enable optimization of such treatment regimens for individual patients revealed favorable clinical and microbiological outcomes. Synergy testing might require for patient whose CRAB has high MIC of both carbapenems and SUL. Further larger scale study is required before endorsing this strategy for routine clinical use.

What is already known on this topic?

Multidrug-resistant (MDR) *A. baumannii* infections have an extremely high crude mortality rate and occur most frequently in hospital acquired infection. Several antimicrobial combination regimens are proposed for improving treatment outcome in MDR *A. baumannii* infected patients. Besides selection of appropriate agent, considering the applications of the

pharmacokinetic-pharmacodynamic (PK-PD) principles are essentials for designing an effective dosing regimens.

What this study adds?

This study aimed to determine the feasibility of MIC determination and synergy testing to guide antimicrobial combination therapy in patients with ventilator-associated pneumonia (VAP) due to carbapenem-resistant *A. baumannii* (CRAB) infections. The results of this study revealed that MIC determination and synergy testing were feasible to perform in clinical setting and achieved impressive treatment outcomes.

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Potential conflicts of interest

None.

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การใช้การทดสอบ MIC และการเสริมฤทธิ์กันในหลอดทดลองสำหรับพิจารณาเลือกยาต้านจุลชีพในการรักษาโรคปอดอักเสบที่เกี่ยวข้องกับเครื่องช่วยหายใจจากการติดเชื้อ Acinetobacter baumannii ที่ดื้อยาคาร์บาพีเนม

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ภูมิหลัง: ข้อมูลการนำผลการศึกษาในหลอดทดลองสำหรับพิจารณาเลือกใช้ยาต้านจุลชีพร่วมกันในทางปฏิบัติมีอยู่จำกัด

วัตถุประสงค์: เพื่อศึกษาความเป็นไปได้และผลลัพธ์ของการประยุกต์ใช้ค่า MIC และการทดสอบการเสริมฤทธิ์กันในหลอดทดลองเพื่อเป็นแนวทางในการรักษาทางคลินิก

วัสดุและวิธีการ: เก็บข้อมูลในผู้ที่ได้รับการวินิจฉัยปอดอักเสบที่เกี่ยวข้องกับเครื่องช่วยหายใจจากการติดเชื้อ A. baumannii ที่ดื้อยาคาร์บาพีเนม ข้อมูลฤทธิ์ในการต้านเชื้อจุลชีพที่ทดสอบด้วยวิธีการ disk diffusion ค่า MIC ของยาต้านจุลชีพและผลการเสริมฤทธิ์กันในหลอดทดลองที่ทดสอบด้วยวิธีการ E-test ถูกนำมาใช้สำหรับพิจารณาเลือกยาต้านจุลชีพเพื่อใช้ร่วมกับโคลิสติน วัดการรักษาที่สิ้นสุดการรักษาด้วยยาต้านจุลชีพ

ผลการศึกษา: ผู้เข้าร่วมวิจัยทั้งสิ้น 10 ราย โดยที่ผู้ป่วย 7 รายได้รับยาต้านจุลชีพแบบคาดการณ์ที่ไม่ครอบคลุมเชื้อ A. baumannii ผลจากการทดสอบในหลอดทดลองด้วยวิธี disk diffusion, การทดสอบ MIC และการทดสอบการเสริมฤทธิ์กันในหลอดทดลอง ทำให้ผู้ป่วยร้อยละ 70, 30 และ 20 ได้รับยาต้านจุลชีพที่คาดว่าน่าจะมีประสิทธิภาพที่ดีต่อการรักษาตามลำดับ ผู้ป่วยจำนวน 9 รายได้รับยาโคลิสตินร่วมกับยาซัลแบคแทมและผู้ป่วย 1 รายได้รับยาโคลิสตินร่วมกับยาอิมิพีเนม ที่สิ้นสุดการรักษาพบว่า ผู้ป่วย 9 รายตอบสนองต่อการรักษาทางคลินิก และผู้ป่วย 6 รายตอบสนองต่อการรักษาทางจุลชีววิทยา

สรุป: ข้อมูลจากการทดสอบ MIC และการเสริมฤทธิ์ในหลอดทดลองด้วยวิธีการ E-test ช่วยเพิ่มโอกาสในการเลือกใช้ยาต้านจุลชีพที่เหมาะสมให้กับผู้ป่วยปอดอักเสบที่เกี่ยวข้องกับเครื่องช่วยหายใจจากการติดเชื้อ A. baumannii ที่ดื้อต่อยาคาร์บาพีเนม วิธีการนี้ให้ผลการรักษาที่ดีและสามารถนำมาใช้ได้จริงในทางปฏิบัติ