In Vitro Susceptibility Pattern of Cephalosporin-Resistant Gram-Negative Bacteria

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Objective: *To determine the in vitro activity of various antimicrobial agents including ertapenem, imipenem, meropenem, fosfomycin, netilmicin, colistin, and piperacillin/tazobactam against clinical isolates of cephalosporin-resistant gram-negative bacteria.*

Material and Method: *All clinical isolates of gram-negative bacteria obtained from patients receiving care at Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand, from 2006-2007 were evaluated for antimicrobial susceptibility. Those resistant to all cephalosporins were further assessed for additional disc susceptibility and MIC test using E-tests.*

Results: *Each of the fifty-five strains of extended spectrum beta-lactamase (ESBL) producing K. pneumoniae and E. coli were tested. The results showed excellent in vitro activity of the studied drugs against ESBL-producing K. pneumoniae with percent susceptibility of 100, 100, 100, 89.8, and 92.7 for ertapenem, imipenem, meropenem, fosfomycin, and colistin, respectively. MIC_{90} of ertapenem, imipenem, meropenem, fosfomycin, and colistin against K. pneumoniae were 0.23, 0.09, 0.38, 59.2, and 0.75 μg/ml, respectively. Piperacillin/tazobactam inhibited 68.2% of the tested isolates of K. pneumoniae. All studied drugs, except netilmicin, exhibited good activity against ESBL-producing Escherichia coli with 100% sensitivity for carbapenem, fosfomycin, colistin and 95.8% for piperacillin/tazobactam. MIC_{90} of ertapenem, imipenem, meropenem, fosfomycin, and colistin against Escherichia coli were 0.177, 0.25, 0.064, 2.85, and 0.58 μg/ml, respectively.*

Six strains of cephalosporin-resistant P. aeruginosa were isolated and tested for MIC. The results showed percent susceptibility of 66.7 and 33.3 for piperacillin/tazobactam and colistin, respectively. MIC_{90} of piperacillin/tazobactam and colistin against P. aeruginosa were 256 and 8 μg/ml, respectively. Twenty-four strains of cephalosporin-resistant Acinetobacter spp. were isolated with percent susceptibility of 17.6 and 95.5 for piperacillin/tazobactam and colistin, respectively. MIC_{90} of piperacillin/tazobactam and colistin against Acinetobacter spp. were 256 and 1.4 μg/ml, respectively.

Conclusion: *Carbapenems, fosfomycin, and colistin exhibited excellent in vitro activity against both ESBL-producing K. pneumoniae and E. coli. Piperacillin/tazobactam exhibited good in vitro susceptibility against ESBL- producing E. coli, but not K. pneumoniae. Colistin was the most potent in vitro activity of antibiotics against cephalosporins-resistant Acinetobacter spp. However, cephalosporin-resistant Pseudomonas aeruginosa remained problematic, we recommend performing in vitro susceptibility test to determine appropriate antibiotic uses. E-test methods have been shown to be more accurate than disc diffusion test for evaluating colistin susceptibility.*

Keywords: *In vitro susceptibility, Gram-negative bacteria, Extended-spectrum beta-lactamase (ESBL), Multi-drug resistance*

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Gram-negative enteric bacteria have emerged as an important pathogen causing nosocomial infection. The wide-spread use of broad spectrum antibiotics such as third generation cephalosporin and carbapenem has resulted in the increased incidence of multi-drug and/or pandrug resistant pathogens[1]. At Queen Sirikit National Institute of Child Health (QSNICH) in 2006, the percentage of susceptibility to imipenem and meropenem were 43% and 31% for *Acinetobacter calcoaceticus baumannii complex* and 81% and 42 % for *P. aeruginosa*, respectively. Although percent susceptibility of extended spectrum beta-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* to carbapenem remains 100% in 2006, we need to closely monitor the MIC level of carbapenem against these pathogens to determine whether there will be an increase in the MIC level leading to treatment failure of carbapenem in the near future. In addition, given the rapid emergence of multi and/or pandrug resistant bacteria, other options of antimicrobial therapy should be assessed for their potential use against these pathogens. In this study, we attempted to identify the current *in vitro* susceptibility of ertapenem, piperacillin/tazobactam, fosfomycin, colistin, imipenem and meropenem against cephalosporin-resistant gram-negative bacteria from clinical isolates of pediatric patients.

Material and Method

All clinical isolates of gram-negative bacteria were evaluated for antimicrobial susceptibility. Those resistant to all cephalosporins were further assessed for additional disc susceptibility and the MIC test using E-tests according to the diagram below (Fig. 1).

ESBL detection test

All clinical isolates of cephalosporin-resistant gram-negative bacteria were obtained from October 2006 to September 2007, and identified by the standard procedures[2]. Briefly, the bacterial inoculum was initially applied to the Mueller-Hinton agar as the

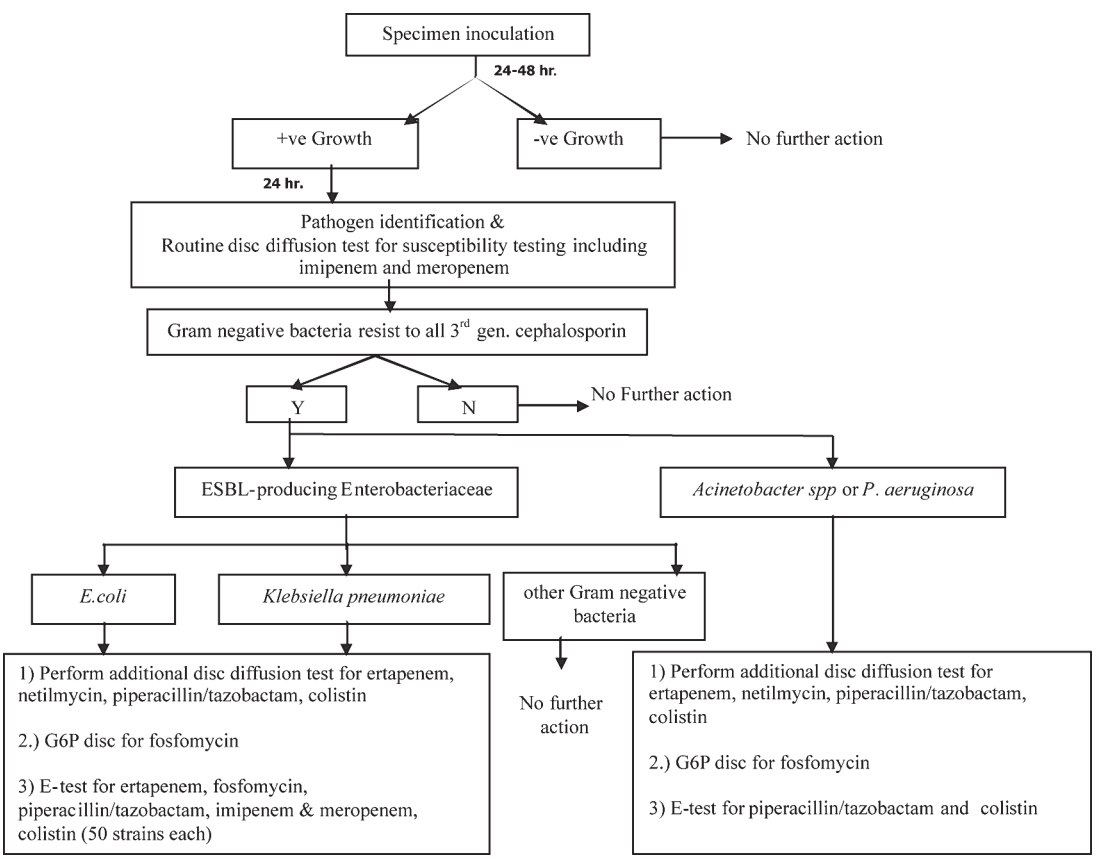

Fig. 1 Flow diagram for determine antimicrobial susceptibility

standard disc-diffusion test. Thirteen antimicrobial discs containing amikacin, ampicillin, cefoperazone/sulbactam, cefotaxime, ceftriaxone, ceftazidime, ciprofloxacin, cotrimoxazole, gentamicin, imipenem, meropenem, netilmicin, and norfloxacin were routinely applied at QSNICH. All cephalosporin-resistant strains were further tested for ESBL production using the combination-disc method[3].

The ESBL production was determined by a more-than-5 mm increase in an inhibition-zone diameter of each antimicrobial disc tested in combination with clavulanic acid, compared with the zone of that antimicrobial disc tested without clavulanic acid. *K. pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 were used for a quality control.

Antimicrobial agents

The following antimicrobial discs were used to determine the susceptibility pattern: ertapenem and imipenem disc from Merk & Co., Inc; the meropenem disc of Astra Zeneca Pharmaceuticals, LP; the fosfomycin disc from Thai Meiji Pharmaceutical Co., Ltd.; the piperacillin/tazobactam disc from Wyeth-Ayerst (Thailand) Ltd.; the colistin disc from Atlantic Pharmaceutical Co., Ltd.

Susceptibility testing

All antimicrobial susceptibility testing was performed using the disc-diffusion method. Ertapenem, imipenem, meropenem, colistin, fosfomycin, and piperacillin/tazobactam were tested for the MIC by E-test method as described by the Clinical Laboratory Standards Institute (CLSI) for ESBL-producing *E. coli* and *K. pneumoniae*[4]. Colistin and piperacillin/tazobactam were also tested for the MIC by E-test method for cephalosporin-resistant strains of *Acinetobacter sp.* and *P. aeruginosa* using the same standard. A quality control was performed by testing *E. coli* ATCC 25922. The MICs of each drug were reported as an MIC range, MIC_{50}, and MIC_{90}.

The clinical isolates of the studied pathogens were obtained from both normally sterile and non-sterile sites. The normally sterile sites included blood, tissue, pleural, peritoneal, joint fluid, and cerebrospinal fluid specimens. The non-sterile sites included purulent discharge, urine, and sputum and bronchoalveolar larvage specimens. Only gram-negative bacteria resisting all third-generation cephalosporin were included in the study. The susceptibility of antimicrobial agents was determined using both disc diffusion and MIC test.

Results

For major ESBL-producing pathogens, a total of fifty-five isolates of *K. pneumoniae* and *E. coli* each were tested in this study. The specimens of the ESBL-producing *K. pneumoniae* from sterile sites included blood (10) or body fluid (6) and non-sterile sites included pus (5), urine (7), wound (2), tracheal suction (20), sputum (2), nasopharyngeal swab (1), and catheter (2). The specimens of the ESBL-producing *E. coli* from sterile sites included blood (7), body fluid (5) and non-sterile sites included pus (5), urine (25), wound (9), tracheal suction (3), and vaginal swab (1) (Table 1, 2).

The results showed the potent *in vitro* activity of carbapenems and colistin according to both disc diffusion and MIC test while piperacillin/tazobactam inhibited only 67.2% of *K. pneumoniae* and 96.7% of *E. coli* according to the MIC test. Fosfomycin appeared to have good *in vitro* activity against these bacteria as well (93.3% and 100% susceptibility by disc diffusion and MIC test for *K. pneumoniae,* respectively and 100% susceptibility by both tests for *E. coli*). MIC_{50} and MIC_{90} of various antimicrobial agents against these two pathogens are shown in Table 3.

According to the MIC_{90} values, meropenem was the most active agent followed by ertapenem. Netilmicin appeared to be ineffective for these pathogens as it exhibited only 12.7% susceptibility by disc diffusion method for both ESBL- producing *K. pneumoniae* and *E. coli*.

Colistin was active against ESBL- producing *K. pneumoniae* with 98.1% and 94.2% susceptibility by the disc diffusion and the MIC method, respectively with MIC_{90} of 0.75 μg/ml. For ESBL-producing *E. coli,* there was 100% susceptibility by both disc diffusion and the MIC method with the MIC_{90} of 0.58 μg/ml.

For non-fermentative gram-negative bacteria, 24 strains of clinical isolated *Acinetobacter spp*. which resisted to all cephalosporins were identified during the study period. For the disc diffusion method, the percent susceptibility against imipenem and meropenem were only 9.1. *In vitro* activities of fosfomycin, netilmicin, piperacillin/tazobactam, and colistin by disc diffusion test were 8.3%, 12.5%, 16.6%, and 100% susceptibility, respectively (Table 4). The MIC_{50} and MIC_{90} for each agent were shown in Table 5.

Six strains of clinical isolated *P. aeruginosa* resistant to all third-generation cephalosporins were obtained during the study period. The specimens of the *P. aeruginosa* from non-sterile sites included urine (3), tracheal suction (2), and colonic fluid (1).

Table 1. Percentage of susceptibility of ESBL-producing *K. pneumoniae* and *E. coli* from the sterile and non-sterile sites against various antimicrobial agents by disc diffusion test

Antimicrobial agents	*K. pneumonia* (n = 55)		*E. coli* (n = 55)	
	Sterile site (n = 16)	Non-sterile site (n = 39)	Sterile site (n = 12)	Non-sterile site (n = 43)
Ertapenem	100	100	100	100
Imipenem	100	100	100	100
Meropenem	100	100	100	100
Netilmicin	0	17.5	33.3	18.6
Fosfomycin	93.3	82.5	100	100
Piperacillin/Tazobactam	66.7	67.5	16.7	83.3
Colistin	100	97.5	100	100

Table 2. Percentage of susceptibility of ESBL-producing *K. pneumoniae* and *E. coli* from the sterile and non-sterile sites against various antimicrobial agents by MIC method

Antimicrobial agents	*K. pneumonia* (n = 55)		*E. coli* (n = 55)	
	Sterile site (n = 16)	Non-sterile site (n = 39)	Sterile site (n = 12)	Non-sterile site (n = 43)
Ertapenem	100	100	100	100
Imipenem	100	100	100	100
Meropenem	100	100	100	100
Fosfomycin	100	91.9	100	100
Piperacillin/Tazobactam	71.4	66.7	100	95
Colistin	100	97.3	100	100

Table 3. Activities of antimicrobial agents clinical isolates of ESBL-producing *K. pneumoniae* and *E. coli*

Antimicrobial agents	MIC (Range)	MIC_{50}	MIC_{90}	Susceptibility (%)
ESBL-producing *K. pneumoniae*				
Ertapenem	0.01-0.38	0.06	0.23	100
Imipenem	0.01-0.38	0.25	0.38	100
Meropenem	0.02-0.19	0.03	0.09	100
Fosfomycin	4-192	16	59.2	89.1
Piperacillin/Tazobactam	3-256	16	256	68.2
Colistin	0.13-48	0.38	0.75	92.7
ESBL-producing *E.coli*				
Ertapenem	0.01-0.75	0.032	0.177	100
Imipenem	0.09-0.38	0.19	0.25	100
Meropenem	0.02-0.125	0.032	0.064	100
Fosfomycin	0.06-48	1	2.85	100
Piperacillin/Tazobactam	0.50-48	3	16.8	95.8
Colistin	0.13-1	0.38	0.58	100

The specimens of the *Acinetobacter spp.* from sterile sites included blood (2), CSF (2), CVP catheter (1) and non-sterile sites included tracheal suction (11), eye discharge (4), urine (2), pus (2). All specimens were resistant to meropenem by disc diffusion method. *In vitro* activity of fosfomycin, netilmicin, imipenem and

Table 4. Percentage of susceptibility of *P. aeruginosa* and *Acinetobacter spp.* from the sterile and non-sterile sites against various antimicrobial agents from disc susceptibility test

Antimicrobial agents	*P. aeruginosa* (n = 6)		*Acinetobacter spp.* (n = 24)	
	Sterile site (n = 0)	Non-sterile site (n = 6)	Sterile site (n = 5)	Non-sterile site (n = 19)
Imipenem	0	60.0	0	11.1
Meropenem	0	0	0	11.1
Netilmicin	0	33.3	20.0	10.5
Fosfomycin	0	33.3	0	10.5
Piperacillin/Tazobactam	0	66.7	20.0	15.8
Colistin	0	100	100	100

Table 5. Activities of antimicrobial agents clinical isolates of *P.aerugionosa* and *Acinetobacter spp.*

Antimicrobial agents	Range	MIC_{50}	MIC_{90}	% susceptibility*		
				% susceptible	% intermediate	% resistant
P. aeruginosa						
Piperacillin/Tazobactam	24-256	48	256	66.7	-	33.3
Colistin	0.38-8.0	5	8	33.3	33.33	33.3
Acinetobacter spp.						
Piperacillin/Tazobactam	0.03-256	256	256	17.7	-	82.4
Colistin	0.19-8	0.5	1.4	95.2	-	4.8

* Susceptibility breakpoint defined by the CSLI: for *P. aeruginosa*:
1. piperacillin/tazobactam: MIC susceptible ≤ 64, resistant ≥ 128;
2. colistin: MIC susceptible ≤ 2, intermediate 4, resistant ≥ 8
Susceptibility breakpoint defined by the CSLI for *Acinetobacter spp.*:
1. piperacillin/tazobactam: MIC susceptible ≤ 16, resistant ≥ 128
2. colistin: MIC susceptible ≤ 2, resistant ≥ 4

piperacillin/tazobactam against these two pathogens were shown in Table 4. The MIC_{50} and MIC_{90} for piperacillin/tazobactam and colistin were shown in Table 5.

Discussion

Carbapenems, fosfomycin and colistin exhibited excellent *in vitro* activity against both ESBL- producing *K. pneumoniae* and *E. coli.* Based on the MIC results, meropenem showed the most potent activity against ESBL-producing *K. pneumoniae*, followed by imipenem, ertapenem, colistin, and fosfomycin, respectively. For ESBL-producing *E. coli*, meropenem was also the most potent antibiotic followed by fosfomycin, imipenem, ertapenem, and colistin, respectively. This high activity of meropenem against ESBL-producing pathogens in Thailand was consistent with reports by Pruekprasert P et al and Hortiwakul R et al[5,6].

Available options besides carbapenem antibiotics were explored for their potential use against these pathogens. The results showed that piperacillin/tazobactam may be used against ESBL- producing *E. coli* but not ESBL- producing *K. pneumoniae* infection because of its low *in vitro* activity against the latter. Netilmicin did not appear to be useful for empirical treatment of either ESBL- producing *K. pneumoniae* or *E. coli* given its low *in vitro* activity. Similar to studies by de Cueto M et al[7], fosfomycin exhibited a good *in vitro* susceptibility pattern against these two pathogens and thus is considered a potential option in case of carbapenem hypersensitivity or failure[7,8]. In addition, it may help avoid selective pressure from the overuse of carbapenems. However, there is not sufficient data comparing clinical effectiveness with carbapenems or other antimicrobial agents against infection caused by these pathogens. Breakthrough resistance is also

an important concern when utilizing fosfomycin. Although colistin appeared to have good *in vitro* activity, it should be considered the last resource in the treatment of gram-negative infections, where no other less toxic or more effective antibiotic is available[9].

Concerning multi-drug resistant non-fermentative gram-negative bacteria, our results demonstrated that colistin had excellent *in vitro* activity against *Acinetobacter spp*. However, its activity against *P. aeruginosa* remained relatively low. We also identified some inconsistencies in the test results between the disc diffusion and the MIC method using E-test. This finding is consistent with the study by Tan TY et al which demonstrated that the disc susceptibility test of colistin remains problematic[10-11]. A study by Gales AC showed that disc susceptibility testing has been documented to be inaccurate, with a high proportion of false susceptibility reports[12]. A study by Arroyo et al found that E-test methods had been shown to be accurate for testing colistin susceptibility in *Acinetobacter spp.*, with over 98% categorical agreement[13]. In addition, standardized disc susceptibility testing methods for colistin from the CLSI in the United States are lacking[10]. Consistent with the previous finding by Tan TY et al[10], resistance to colistin appears to be relatively high in *P. aeruginosa* at our institute. Therefore, we suggested that universal susceptibility to the colistin should not be assumed, particularly for *P. aeruginosa*. Piperacillin/tazobactam showed a higher susceptibility rate than colistin against multi-drug resistant *P. aeruginosa.* Thus, it might be more useful in treating infections caused by this pathogen. On the other hand, colistin appeared to be a better option for the treatment of infections caused by multi-drug resistant *Acinetobacter spp.* Nevertheless, the application of this finding requires the consideration of current local susceptibility data of individual hospitals. Long-term monitoring of the susceptibility pattern of clinically important pathogens is, thus, essential for the proper use of antimicrobial therapy in clinical practice.

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ความไวต่อยาปฏิชีวนะของเชื้อแบคทีเรียรูปแท่งกรัมลบที่ดื้อต่อcephalosporin

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วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพทางห้องปฏิบัติการของยาต้านจุลชีพ ertapenem, imipenem, meropenem, netilmycin, piperacillin/tazobactam, fosfomycin และ colistin ต่อเชื้อแบคทีเรียกรัมลบที่ดื้อต่อ cephalosporin*

วัสดุและวิธีการ: *เชื้อกรัมลบที่ดื้อต่อยาทุกตัวในกลุ่ม cephalosporin ที่แยกได้จากผู้ป่วยที่เข้ารับการรักษา ที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินีระหว่าง ตุลาคม พ.ศ. 2549 - กันยายน พ.ศ. 2550 ได้รับการวัดหาค่าความไวด้วยวิธี disc diffusion test และระดับ MIC*

ผลการศึกษา: *ESBL- producing K. pneumoniae และ E. coli จำนวนอย่างละ 55 สายพันธุ์ได้รับการทดสอบพบว่า ESBL-producing K. pneumoniae มีความไวต่อยา กลุ่ม carbapenems ได้แก่ ertapenem, imipenem, meropenem, fosfomycin และ colistin ดี โดยมี percent susceptibility เท่ากับ 100, 100, 100, 89.8, and 92.7 ตามลำดับ โดย MIC90 of ertapenem, imipenem, meropenem, fosfomycin, และ colistin ต่อ K. pneumoniae เท่ากับ 0.23, 0.09, 0.38, 59.2, และ 0.75 μg/ml ตามลำดับ ในขณะที่ piperacillin/tazobactam ยับยั้งเพียง 68.2% ของเชื้อ K. pneumoniae ที่แยกได้ ยาทุกตัวที่ศึกษายกเว้น netilmicin มีฤทธิ์ครอบคลุมเชื้อ t ESBL-producing E. coli โดยมีความไวเท่ากับ 100% ต่อ carbapenem, fosfomycin, colistin และ 95.8% ต่อ piperacillin/tazobactam MIC_{90} ของ ertapenem, imipenem, meropenem, fosfomycin, และ colistin ต่อ E. coli เท่ากับ 0.177, 0.25, 0.064, 2.85, และ 0.58 μg/ml ตามลำดับ cephalosporin-resistant Acinetobacter spp. ทั้งหมด 24 ตัวอย่าง ได้รับการวิเคราะห์ความไวต่อยาปฏิชีวนะ พบว่ามีความไวต่อ piperacillin/tazobactam and colistin เท่ากับ 66.7% และ 33.3% ตามลำดับ โดยมี MIC_{90} ของ ยาดังกล่าว เท่ากับ 256 and 8 μg/ml ตามลำดับ สำหรับ cephalosporin-resistant P. aeruginosa ทั้งหมด 6 สายพันธุ์มีความไวต่อ piperacillin/tazobactam และ colistin เท่ากับ 17.6 and 95.5 ตามลำดับ โดยมี MIC90 ของ ยาดังกล่าวเท่ากับ 256 and 1.4 μg/ml ตามลำดับ*

สรุป: *ESBL- producing K. pneumoniae และ E. coli ยังคงมีค่าความไวต่อยาค่อนข้างดีต่อกลุ่ม carbapenems, fosfomycin และ colistin ในขณะที่ piperacillin/tazobactam ออกฤทธิ์ดีต่อ ESBL- producing E. coli, แต่มีประสิทธิภาพต่ำสำหรับ K. pneumoniae colistin เป็นยาที่มีประสิทธิภาพดีต่อ cephalosporin-resistant Acinetobacter spp. แต่ฤทธิ์ในการครอบคลุม cephalosporin-resistant P. aeruginosa ยังไม่ค่อยดีนักจึงจำเป็นต้องทำการตรวจยืนยันประสิทธิภาพทางห้องปฏิบัติการโดยเฉพาะอย่างยิ่งโดยการทำ MIC ด้วย E-test เนื่องจากการตรวจวิธีนี้จะให้ผลที่แม่นยำกว่าวิธี disc diffusion test*