Original Article

The Combination Antibiogram Evaluation for Antimicrobial Susceptibility of Carbapenem-Resistant *Klebsiella pneumoniae* and Carbapenem-Resistant *Escherichia coli*

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Background: The incidence of carbapenem-resistant enterobacterales (CRE), *Escherichia coli* and *Klebsiella pneumoniae* increased twofold and tenfold within the past 20 years, respectively. CRE is resistant to most antibiotics and monotherapy cannot provide greater than 90% coverage. Combination antimicrobial regimen is introduced to increase the susceptibility rate and to recommend clinicians to make more informed decision in the selection of empirical therapy.

Materials and Methods: Cross-sectional study on carbapenem-resistant *E. coli* and carbapenem-resistant *K. pneumoniae* isolated from blood, sputum, and urine of adult inpatients in Naresuan University Hospital were examined for 24 months, between January 1, 2018 and December 31, 2019. The susceptibility data were formulated in accordance with the Clinical and Laboratory Standards Institute M39 guidelines and the combination antibiogram was developed. Chi-square test and Fisher's exact test were used to determine the differences in susceptibility rates.

Results: Forty-three isolates of the carbapenem-resistant *E. coli* and 208 isolates of the carbapenem-resistant *K. pneumoniae* were included for the analysis. More CRE organisms were found in the Internal Medicine than in the non-Internal Medicine wards. Monotherapy regimen with amikacin was shown to cover 97.67% of the *E. coli* CRE in vitro and when used as an additional agent as meropenem plus amikacin, imipenem plus amikacin, piperacillin-tazobactam plus amikacin, or levofloxacin plus amikacin, which all the percent susceptible increased to 97.67% ($p<0.001$). The *K. pneumoniae* CRE data showed that only 1.92% was susceptible to meropenem. Meropenem plus gentamicin, imipenem plus gentamicin, piperacillin-tazobactam plus gentamicin and levofloxacin plus gentamicin could increase the percent susceptibility but to less than 90% with $p<0.001$.

Conclusion: Aminoglycosides are the proposed addition for the empiric antimicrobial combination therapy to treat possible CRE infections. Meropenem plus amikacin, imipenem plus amikacin, piperacillin-tazobactam plus amikacin, or levofloxacin plus amikacin are proposed to use against *E. coli* CRE. No combination therapy is recommended for *K. pneumoniae* CRE.

Keywords: Enterobacteriaceae; Carbapenem-resistant *Klebsiella pneumoniae*; Carbapenem-resistant *Escherichia coli*; CRE; Antimicrobial susceptibility; Combination antibiogram

Received 13 December 2021 | Revised 14 February 2022 | Accepted 22 February 2022

J Med Assoc Thai 2022;105(5):466-71

Website: http://www.jmatonline.com

Antimicrobial resistance has become a new global challenge. In 2050, mortality from this problem is expected to reach 10,000,000 cases[1]. In Thailand, there are 87,751 antimicrobial-resistant cases every year and 40% of them die[2]. Inappropriate use of antibiotics can statistically increase the mortality rates, hospital stays, and medical costs[3].

Between 2000 and 2019, the rate of carbapenem-resistant *Escherichia coli* cases has doubled while the rate of carbapenem-resistant *Klebsiella pneumoniae* has increased tenfold in Thailand[4]. Gram-negative pathogens that are resistant to carbapenem are called carbapenem-resistant enterobacterales (CRE). Furthermore, they resist to commonly used antibiotics such as penicillin, and third and fourth generations of cephalosporin[5]. Thus, the appropriate use of antibiotics for empirical treatment to CRE pathogens is often challenging and a combination regimen

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How to cite this article:

Boonsirichan S, Wannalerdsakun S. The Combination Antibiogram Evaluation for Antimicrobial Susceptibility of Carbapenem-Resistant *Klebsiella pneumoniae* and Carbapenem-Resistant *Escherichia coli*. J Med Assoc Thai 2022;105:466-71.

DOI: 10.35755/jmedassocthai.2022.05.13304

is introduced to increase the susceptibility. A retrospective analysis of more than 5,000 specimens showed that the addition of a second antibiotics could statistically increase the coverage ($p<0.1$)[6]. Another retrospective study in *Pseudomonas aeruginosa*, a main pathogen in the United States, showed that the combination regimen was more effective than the monotherapy[7]. A Thai retrospective study in Rajavithi Hospital between 2009 and 2015 found that *K. pneumoniae* was the most causative CRE[8] and the increasing use of levofloxacin might be the reason[9]. The use of inappropriate antibiotics in severe patients increased the mortality three-times[10]. One study showed that the mortality rate of patients who received monotherapy (54%) was significantly higher than that with combination therapy (34%) and the combination therapy was reported to have the greatest effect on survival rates in critically-ill patients[11].

As a result, there are limited studies about combination regimen to *E. coli* CRE and *K. pneumoniae* CRE in Thailand. The present study objective was to evaluate the combination regimen of antimicrobial susceptibility of carbapenem-resistant *E. coli* and carbapenem-resistant *K. pneumoniae*.

Materials and Methods

The present study was a cross-sectional study in adult patients, older than 18 years of age, from both the Internal Medicine and the non-Internal Medicine wards admitted at Naresuan University Hospital between January 1, 2018 and December 31, 2019. The authors excluded the specimens obtained from the pediatrics department and the similar pathogen arisen from the same source in the same patient within 30 days. The authors examined the data of these two pathogens from three main specimen sources, namely blood, sputum, and urine.

The incubations and the susceptibility were referenced to the CLSI protocols. CRE pathogens referred to the pathogens that were resistant to either imipenem, meropenem, ertapenem, or doripenem[12].

Ethical approval for the present study was obtained from Naresuan University Institutional Review Board (P3-0112/2563).

Statistical analysis

The susceptibility data were formulated according to the Clinical and Laboratory Standards Institute (CLSI) M39 guidelines[13] and the combination antibiograms were then developed. Continuous data were shown as median and categorical data were shown as frequency and percentage. Chi-squared test and Fisher's exact test were used to determine the differences in susceptibility or resistance rates for these selected organisms. The Fisher's exact test was used when the data set failed to fulfill Chi-squared test requirements. A p-value of less than 0.05 is statistically significant. The Stata, version 12.1 (StataCorp LP, College Station, TX, USA) was used in the statistical analysis.

Antibiotics were selected for the present study and included ceftriaxone as a representative of third generation cephalosporin, cefepime as a representative of forth generation cephalosporin, piperacillin-tazobactam as a representative of betalactam-betalactamase inhibitor, meropenem and imipenem as representatives of carbapenem, amikacin and gentamicin as representatives of aminoglycosides, and levofloxacin as a representative of fluoroquinolone. Colistin was not included because colistin employs minimal inhibitory concentrations (MIC) to determine its susceptibility while the others use a disc diffusion method. Antibiotics from the same group would not be used to compare and calculate the percent susceptibility (%Susceptible). In accordance with the CLSI M39-A4:2014, a minimum of 30 specimens is needed to calculate the percent susceptibility of the pathogen.

Results

The present retrospective study examined all the isolates in Naresuan University Hospital for 24 consecutive months and *E. coli* CRE and *K. pneumoniae* CRE were used in the analysis. There were initially 50 specimens for *E. coli* CRE and 371 specimens for *K. pneumoniae* CRE. After removing the duplications, there were 43 specimens for *E. coli* CRE and 208 specimens for *K. pneumoniae* CRE.

Twenty-nine *E. coli* CRE isolates (67.44%) were obtained from the Internal Medicine wards and 14 isolates (32.56%) were from the non-Internal Medicine wards, namely from surgery, orthopedics, obstetrics-gynecology, otorhinolaryngology, and ophthalmology. There were six samples (13.95%) from blood, seven samples (16.28%) from sputum, and 30 samples (69.77%) from urine. The median patient age was 68 years old, with a range between 19 and 90 years old. One hundred thirty-three *K. pneumoniae* CRE cases (63.94%) were from the Internal Medicine ward while 75 cases (36.06%) were from the others. Twelve samples (5.77%) were from blood, 74 samples (35.58%) were from sputum, and 122 samples (58.68%) were from urine. The median patient age was 72 years, with a range between 20

Table 1. Pathogens' characteristics from different wards and different specimens

Pathogens	Wards; n (%)		Specimens; n (%)			Age (years)		
	Internal Medicine	Non-Internal Medicine	Blood	Sputum	Urine	Minimum	Maximum	Median
E. coli (n=43)	29 (67.44)	14 (32.56)	6 (13.95)	7 (16.28)	30 (69.77)	19	90	68
K. pneumoniae (n=208)	133 (63.94)	75 (36.06)	12 (5.77)	74 (35.58)	122 (58.65)	20	102	72

Table 2. Single agent antibiogram results for *Escherichia coli* CRE and *Klebsiella pneumoniae* CRE isolates

Organism	%Susceptible (single agent antibiogram)							
	Ceftriaxone	Cefepime	Piperacillin-tazobactam	Meropenem	Imipenem	Amikacin	Gentamicin	Levofloxacin
E. coli (n=43)	0.00	0.00	4.65	9.30	9.30	97.67	34.88	6.98
K. pneumoniae (n=208)	0.00	0.00	0.96	1.92	4.81	38.94	58.17	1.44

Table 3. Combination antibiogram for *Escherichia coli* CRE (n=43)

E. coli	Monotherapy	Imipenem			Amikacin			Gentamicin			Piperacillin-tazobactam			Levofloxacin		
	%S	n	%S	n	p-value	%S	n	p-value	%S	n	p-value	%S	n	p-value	%S	n	p-value
Meropenem	9.30	4	11.63	5	0.500#	97.67	42	<0.001#*	44.19	19	<0.001*	9.30	4	1.000#	16.28	7	0.260#
Imipenem	9.30	4		N/A	N/A	97.67	42	<0.001#*	44.19	19	<0.001*	11.63	5	0.500#	16.28	7	0.260#
Amikacin	97.67	42	97.67	42	0.753#		N/A	N/A	100	43	0.500#	97.67	42	1.000#	97.67	42	1.000#
Gentamicin	34.88	15	44.18	19	0.378	100	43	<0.001#*		N/A	N/A	39.53	17	0.655	34.88	15	1.000
Piperacillin-tazobactam	4.65	2	11.63	5	0.217#	97.67	42	<0.001#*	39.53	17	<0.001*		N/A	N/A	11.63	5	0.217#
Levofloxacin	6.98	3	16.28	7	0.157#	97.67	42	<0.001#*	34.88	15	<0.001*	11.63	5	0.356#		N/A	N/A

N/A=not applicable

p-value was calculated by Fisher's exact test, * Statistically significant

and 102 years old. This data is presented in Table 1.

Table 2 shows the single agent antibiogram results for *E. coli* CRE and *K. pneumoniae* CRE. Ceftriaxone and cefepime, which were the representatives of cephalosporin group, had no susceptibility. Piperacillin-tazobactam, meropenem, and levofloxacin had very low susceptibility, whereas aminoglycosides achieved the most susceptibility. The %Susceptible of amikacin and gentamicin to *E. coli* CRE were 97.67% and 34.88%, respectively, while the %Susceptible of amikacin and gentamicin to *K. pneumoniae* CRE were 38.97% and 58.17%, respectively. An antibiotic must be able to provide a %Susceptible of more than 90% to be used as an empirical therapy.

It was worthy to note that amikacin alone had a significant impact as a monotherapy, and could already cover 97.67% regardless of the choice for the second antimicrobial agent for the combination regimen. The addition of amikacin as a second antimicrobial agent to meropenem, imipenem, piperacillin-tazobactam, and levofloxacin in *E. coli* CRE could achieve %Susceptible to more than 90% ($p<0.001$). Gentamicin could also be used as the additional antimicrobial but increased the %Susceptible to a lesser extent from 34.88% to 44.18% ($p<0.001$). Other combination regimen could also increase the %Susceptible but with no statistical significance (Table 3).

The %Susceptible of the combination regimen of *K. pneumoniae* CRE was similar to that of *E. coli* CRE. The addition of gentamicin to meropenem, imipenem, piperacillin-tazobactam, and levofloxacin would increase %Susceptible from 77.40% to 79.33% ($p<0.001$). Amikacin as the second antimicrobial agent could increase %Susceptible to a lesser extent from 48.08% to 48.56% ($p<0.001$). Piperacillin-tazobactam plus imipenem could increase %Susceptible from 0.96% to 4.81% ($p=0.019$) whereas levofloxacin plus imipenem could increase %Susceptible from 1.44% to 6.25% ($p=0.011$). No combination regimen achieved more than 90% coverage (Table 4).

Discussion

CRE pathogens in Naresuan University Hospital were found in the Internal Medicine wards more than in the Non-Internal Medicine wards and the most common source was from urine, which were

Table 4. Combination antibiogram for *Klebsiella pneumoniae* CRE (n=208)

K. pneumoniae	Monotherapy		Imipenem			Amikacin			Gentamicin			Piperacillin-tazobactam			Levofloxacin		
	%S	n	%S	n	p-value	%S	n	p-value	%S	n	p-value	%S	n	p-value	%S	n	p-value
Meropenem	1.92	4	4.81	10	0.103	48.08	100	<0.001*	77.88	162	<0.001*	2.40	5	0.500#	3.85	8	0.241
Imipenem	4.81	10		N/A	N/A	48.56	101	<0.001*	79.33	165	<0.001*	4.81	10	1.000	6.25	13	0.520
Amikacin	38.94	81	48.08	100	0.060		N/A	N/A	94.23	196	<0.001*	48.08	100	0.060	48.08	100	0.060
Gentamicin	58.17	121	79.33	165	<0.001*	94.23	196	<0.001*		N/A	N/A	77.40	161	<0.001*	78.37	163	<0.001*
Piperacillin-tazobactam	0.96	2	4.81	10	0.019*	48.08	100	<0.001*	77.4	161	<0.001*		N/A	N/A	2.40	5	0.225#
Levofloxacin	1.44	3	6.25	13	0.011*	48.08	100	<0.001*	78.37	163	<0.001*	2.40	N	0.362#		N/A	N/A

N/A=not applicable

p-value was calculated by Fisher's exact test, * Statistically significant

consistent with the previous study[7].

Ceftriaxone and cefepime showed no susceptibility to both CREs. For *E. coli* CRE, the %Susceptible of piperacillin-tazobactam, meropenem, imipenem, and levofloxacin were at 4.65%, 9.30%, 9.30%, and 6.98%, respectively (Table 2). For *K. pneumoniae* CRE, the %Susceptible of piperacillin-tazobactam, meropenem, imipenem, and levofloxacin were all below 5%. Thus, these antimicrobial groups were not recommended to use as an empirical therapy in the patients with suspected CRE infections even when the %Susceptible of amikacin and gentamicin in *K. pneumoniae* CRE were at 38.94% and 58.17%, respectively. These results were consistent with CRE characteristics, which were resistant to antimicrobial groups and offered low %Susceptible. In addition, the single agent of amikacin in the present study showed to have a remarkably high %Susceptible of 97.67% for *E. coli* CRE. Nevertheless, the practitioners might not use aminoglycosides group to treat bloodstream infections because they often fail to offer good clinical outcomes. The aminoglycosides will be used only as a last resort[14].

The present study also showed that the combination regimen could indeed increase %Susceptible. Monotherapy regimen with amikacin was shown to provide 97.67% coverage for the *E. coli* CRE in vitro and when used as an additional agent such as meropenem plus amikacin, imipenem plus amikacin, piperacillin-tazobactam plus amikacin, or levofloxacin plus amikacin, all %Susceptible showed to be equal to or greater than 97.67% ($p<0.001$). These four combination regimens were recommended to use as an empirical therapy in patients with suspected *E. coli* CRE infections.

The data of *K. pneumoniae* CRE showed that only 1.92% was susceptible to meropenem and none of the combinations such as imipenem plus gentamicin, piperacillin-tazobactam plus gentamicin, or levofloxacin plus gentamicin, could achieve a coverage greater than 90% despite the statistical significance.

The combination regimen that uses more than one antibiotic in treating patients with CRE infections is more useful than the single regimen in severe infections because it increases synergistic effects of antibiotics and decreases the possibility of drug resistance. However, cautious use of the combination regimen is recommended due to the increase in potential side effects[15] especially when aminoglycosides are prescribed[16]. A low dose of gentamicin can affect the renal functions[17] and cause hearing impairments[18].

The present study limitations are that the susceptibility of different antibiotics to different pathogens might be inaccurate due to the different timing of specimen collections. In addition, this was a single study in one hospital. Furthermore, Naresuan University Hospital might have different local drug resistance profile than other hospitals. In the present study, there were not many *E. coli* CRE during this 24-month period and carried-out in vitro thus the side effects of using combination regimens were not assessed. In addition, there were other factors such as patients' underlying medical conditions and patients' history of antibiotics exposure, affecting the decisions on which was the most appropriate empirical antimicrobial therapy. Another limitation is that the present study did not take the patients' previous antimicrobial medication history, thus, the authors could not conclude the main reason for the CRE prevalence. Other studies found that the resistance to fluoroquinolone in *E. coli* and *K. pneumoniae* was the main factor for the increasing mortality[19]. Other risk factors were male gender, chronic lung diseases, recent hospitalization within two weeks and previous antimicrobial therapy of fluoroquinolone, cotrimoxazole, and metronidazole[20].

This is consistent with other studies which found that previous usage of ceftriaxone, ceftazidime, fluoroquinolone, aminoglycoside, cotrimoxazole, vancomycin, and metronidazole would increase the possibility of having the drug-resistant *E. coli* and *K. pneumoniae*[21]. Moreover, our study did not assess the genes due to limited resources and did not include colistin in our analysis. One study in China showed that the triple antimicrobial combinations of meropenem-tigycycline-colistin had a synergistic effect of 100%[22]. Colistin could also be another potential additional antibiotic for the combination regimen. Future studies are recommended to include the patients' previous antimicrobial therapy in their analyses. The present study did not receive any funding.

Conclusion

The present study results show that the aminoglycosides are a good addition for the empirical antimicrobial combination therapy when carbapenem-resistant infections are suspected. Meropenem plus amikacin, imipenem plus amikacin, piperacillin-tazobactam plus amikacin, or levofloxacin plus amikacin are proposed to use against the *E. coli* CRE. No combination therapy is recommended for the *K. pneumoniae* CRE. Further studies are needed to follow the trends of constantly changing antibiograms and different hospitals may represent different antibiograms. In addition, the present study acts as a recommendation guideline for empirical therapy and care providers should then select the appropriate antibiotics in accordance with the reported organism's antibiotic sensitivity profile.

What is already known on this topic?

The combination antimicrobial regimen can increase the susceptibility and coverage rate particularly in the CRE.

What this study adds?

The aminoglycosides are a good addition for the empirical antimicrobial combination therapy when carbapenem-resistant infections are suspected. Combination regimens are recommended for *E. coli* CRE while no combination therapy is recommended for the *K. pneumoniae* CRE.

Acknowledgement

The completion of the present study was possible with the support of the Internal Medicine medical staffs of the Naresuan University Hospital. The authors wish to express their gratitude to their beloved families and friends who served as our inspiration and motivators.

Conflicts of interest

The authors declare no conflict of interest.

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