Analysis Xpert[®]-Carba-R on Carbapenem Resistant *Enterobacterales* Screening in Intensive Care Unit in National Referral Hospital in Jakarta

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Abstract

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Introduction: Carbapenem-resistant Enterobacterales (CRE) represent a significant global health problem due to their high resistance to antibiotics. Traditional methods for identifying resistance genes, such as Real-Time PCR (RT-PCR), are accurate but time-consuming and involve complex techniques. This study aimed to compare the Cepheid Xpert® Carba-R test with RT-PCR, used as the gold standard, to determine its effectiveness in rapidly identifying carbapenem resistance genes in CRE.

Method: The study was performed from January to June 2022, involving patients admitted to the Intensive Care Unit (ICU) at Dr. Cipto Mangunkusumo National Hospital. Rectal or perirectal swabs were collected upon ICU admission. If patients tested negative for CRE upon admission, repeat swabs were taken at discharge or death, with a maximum length of stay (LOS) of 14 days in the ICU. Genotypic identification of carbapenem resistance genes, including KPC, NDM, OXA-48, VIM, and IMP, was performed using the Cepheid Xpert[®] Carba-R and compared to RT-PCR. Additionally, phenotypic identification through bacterial culture was performed using the Vitek method.

Result: Out of 102 ICU patients, 10.23% (22/215 isolates) were found to be positive for CRE, with the most common bacterial isolates being Escherichia coli (148/215, 68.83%) and Klebsiella pneumoniae (53/215, 24.65%). CRE was found in 1 of 148 E. coli isolates (0.67%) and in 21 of 53 K. pneumoniae isolates (39.62%). The most frequently detected carbapenem resistance gene was OXA-48 (16/22, 72.73%), followed by NDM (6/22, 27.27%). The Xpert[®] Carba-R test demonstrated a sensitivity and specificity of 100%, with positive predictive value (PPV) and negative predictive value (NPV) both equal to 1. A discrepancy was observed between the phenotypic and genotypic identification, with 27 phenotypically identified CRE isolates compared to 22 genotypically confirmed ones.

Conclusion: The Cepheid Xpert[®] Carba-R test provides a reliable, rapid alternative for identifying carbapenem resistance genes in CRE, demonstrating perfect sensitivity and specificity in this study. This study indicates that Xpert[®] Carba-R can be an alternative in the rapid identification of CRE resistance genes.

Keywords: CRE, Real-Time PCR, Xpert® Carba-R, Culture, Sensitivity, Specificity.

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Introduction

Carbapenems are among the most potent beta-lactam antibiotic, commonly used against infections caused by multidrug-resistant bacteria. However, carbapenem resistance in gram-negative bacteria, particularly in the Enterobacterales group, has become a growing concern in healthcare settings. These bacteria produce specific enzymes that deactive carbapenems, thus reducing treatment options.¹ Surveillance data has shown a steady rise in disease due to Carbapenem-Resistant *Enterobacterial* (CRE) infections. In 2013, the Centers for Disease Control and Prevention (CDC) estimated that CRE infections affected 9,300 patients annually, with a mortality rate of 6,6%. Globally, the prevalence of carbapenem-resistant *Klebsiella pneumoniae* varies, with the WHO reporting rates as high as 68% in Europe and as low as 3.5% in Africa as of 2014.² In Indonesia, carbapenem resistance in ICU patients has also shown a noteworthy rise. A 2008 study in Jakarta indicated carbapenem resistance in *Pseudomonas aeruginosa* (21.9%), Enterobacterales (27.6%), and *Acinetobacter baumannii* (50.5%).³ By 2013, 5.3% of *K. pneumoniae* isolates harbored the New Delhi Metallo-beta-lactamase (NDM) gene, with 9.5% acquired during hospitalization in Indonesia.⁴ Early detection of CRE is critical for controlling its spread and reducing mortality. Culture-based identification of CRE is time-consuming, often taking several days. Conversely, nucleic acid-based methods, such as *polymerase chain reaction* (PCR), offer faster results by targeting specific resistance genes.⁵ The sensitivity and specificity of PCR were 96.3% and 99.6%, respectively.⁶ The main advantages of nucleic acid-based molecular tests compared to conventional cultures are faster and more effective identification of CRE in clinical settings.²

Early detection of CRE is important for infection prevention and control programs and prevent further spread of CRE. Molecular tests such as Xpert Carba-R are vital for early detection of CRE. This study aims to compare the performance of the Xpert[®] Carba-R rapid molecular test with Real-Time PCR, considered the gold standard for detecting carbapenem resistance genes in ICU patients at Dr. Cipto Mangunkusumo National Hospital in Jakarta, Indonesia.

Material and Methods

Study Design and Setting

This anlytical observational study, employing a cross-sectional design, was conducted in the ICU of Dr. Cipto Mangunkusumo National General Hospital and the Clinical Microbiology Laboratory of the Faculty of Medicine, Universitas Indonesia.

Study Population

The study included ICU patients from January to June 2022. Patients were included based on these inclusion criteria: age ≥ 18 years, admitted to the ICU within 24 hours, agreed to rectal/perirectal swab collection. Informed consent was obtained from patients or their families. Patients were excluded if clinical data were incomplete or they opted out of participation.

Bacterial Isolates

Rectal or perirectal swab specimens were collected from patients within the first 24 hours of ICU admission using Amies transport media, based on CDC guidelines. Patients who were not colonized with multidrug-resistant gram-negative bacteria upon admission were retested upon discharge or death, with a maximum ICU stay of 14 days.

Identification

The swab samples were initially tested using the Xpert[®] Carba-R to directly identify CRE-specific resistance genes. Following this, the samples were inoculated on MacConkey agar for culture.

Phenotypic identification and the susceptibility testing were performed using the Vitek2 system (bioMérieux), with resistance breakpoints defined by the CLSI: meropenem MIC >16 mg/L or ertapenem MIC >8 mg/L.

Genotypic identification of resistance genes (KPC, NDM, OXA-48, VIM, IMP) was performed using RT-PCR. The results from RT- PCR were compared to those obtained from the Xpert[®] Carba-R.

Sample Size

 $n_{Sen} =$

90,61

Sample size was calculated based on this formula:

$$n_{Sen} = \frac{Z\alpha^{2} sen (1 - sen)}{d^{2}P}$$

$$n_{Sen} = \frac{1,96^{2} x \ 0.93 x (1 - 0.93)}{0.1^{2} x \ 0.276} \qquad n_{Sen} = \frac{1.96^{2} x \ 0.93 x (0.07)}{0.01 x \ 0.276}$$

Based on the above formula, added with 10% correction, the sample size needed was 100 samples.

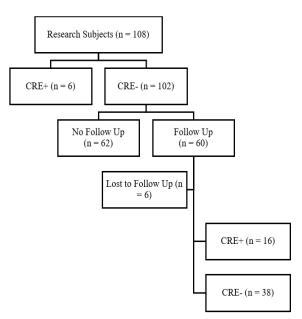


Figure 1. Subject Recruitment Flowchart and Sampling Results

Results

There were 108 patients included at the beginning of the study. However, there were six subjects who could not be followed up and were excluded. Thus, the final number of subjects analyzed in this study was 102 patients. (Figure 1)

Baseline characteristics of the patients admitted to ICU at RSCM are shown in table 1.

while the proportion of CRE-positive isolates was 10.23% (22/215).

The most common microorganisms identified were *Escherichia coli* and *Klebsiella pneumoniae* ssp pneumoniae, while other microorganisms identified in small numbers. In the initial screening, 7 (4.35%) samples had negative results and in the follow-up screening, 8 (11.59%) samples showed no growth. The most common resistance genes detected were NDM (27.3%) and OXA-48 (72.7%) in table 2.

Chanadariation	CRE+ CRE-		Total	
Characteristics	(n = 22)	(n = 80)	(n=102)	
Age [year, mean]	$47,73 \pm 15,7$	$47,51 \pm 18,8$	$47,56 \pm 18,1$	
Gender, n (%)				
Male	11 (50)	45 (56,2)	56 (54,9)	
Female	11 (50)	35 (43,8)	46 (45,1)	
LOS prior ICU admission [day, median]	2 (0 - 24)	3 (0 – 31)	2 (0-31)	
Origin of ICU, n (%)				
ICU Kiara	8 (36,4)	33 (41,3)	41 (40,2)	
ICU Emergency Department	13 (59,1)	26 (32,5)	39 (38,2)	
ICU Adult	1 (4,5)	21 (26,3)	22 (21,6)	
Hospitalization history > two days within the last six months n (%)	8 (36,4)	35 (43,8)	43 (42,2)	
Referral History from other Hospitals n (%)	5 (22,7)	15 (18,8)	20 (19,6)	
Comorbidity, n (%)				
Sepsis	9 (40,9)	33 (41,3)	42 (41,2)	
COVID-19	7 (31,8)	34 (42,5)	41 (40,2)	
Hypertension	8 (36,4)	29 (36,3)	37 (36,3)	
Diabetes Mellitus	10 (45,5)	24 (30,0)	34 (33,3)	
Chronic Kidney Disease	9 (40,9)	19 (23,8)	28 (27,5)	
Cancer	3 (13,6)	19 (23,8)	22 (21,6)	
Congestive Heart Failure	6 (27,3)	11 (13,8)	17 (16,7)	
Hemodialysis	4 (18,2)	7 (8,8)	11 (10,8)	
Coronary Artery Disease	3 (13,6)	7 (8,8)	10 (9,8)	
COPD	2 (9,1)	6 (7,5)	8 (7,8)	
Chronic Liver Disease	1 (4,5)	5 (6,3)	6 (5,9)	
Antibiotic use history in the last 3 Months, n (%)	20 (90,9)	73 (91,3)	93 (91,2)	
Meropenem prescription, n (%)	7 (31,8)	17 (21,3)	24 (23,5)	

Table 1. Characteristics of Patients Admitted to ICU at RSCM between January - June 2022

Abbreviations: CRE, Carbapenem-Resistant Enterobacterial; ICU, intensive care unit; LOS, length of stay; COVID-19, corona virus disease-2019; COPD, Chronic obstructive pulmonary disease.

Prevalence and Distribution of CRE

In the screening conducted at the time of initial admission to the ICU, 102 subjects were examined, yielding 154 isolates. Seven samples showed no bacterial growth. During the follow-up screening on 54 subjects, 61 isolates were collected, with eight samples showing no growth. The proportion of CRE-positive patients was 21.57% (22/102), The study examined the distribution of carbapenem-resistant (CR) microorganisms using both phenotypic (Vitek method) and genotypic (Xpert Carba-R Molecular Test) screening methods. In the phenotypic screening, the initial examination identified 9 CR-positive isolates out of 154, resulting in a CR prevalence of 5.84% per isolate, and 9 out of 102 patients were CR-positive, yielding a prevalence of 8.82% per patient. The

Table 2. Distribution of genes Among CRE

	Microorganism	Resistance genes	Total
	Escherichia coli	NDM	1
Admission	Klebsiella pneumoniae	NDM	3
		OXA-48	2
Follow Up	Klebsiella	NDM	2
	pneumoniae	OXA-48	14

follow-up screening identified 18 out of 61 isolates were CR-positive, resulting in a CR prevalence of 29.51% per isolate, while 18 out of 54 patients were CR-positive, with a prevalence of 33.33% per patient. The combined data from both screening showed a total CR prevalence of 12.56% per isolate and 26.47% per patient. (Table 3)

The phenotypic screening revealed that, during the initial screening, 8 out of 154 isolates were CRE-positive, resulting in a prevalence of 5.19% per isolate, and 8 out of 102 patients were CRE-positive, with a prevalence of 7.84% per patient. In the follow-up screening, 16 out of 61 isolates were CRE-positive, with a prevalence of 26.23%, and 16 out of 54 patient were CRE-positive, leading in a prevalence of 29.63%.

In terms of genotypic screening with the Xpert Carba-R Molecular Test, 6 out of 154 isolates were CRE-positive in the initial screening, resulting to a CRE prevalence of 3.90% per isolate and 5.88% per patient. In the follow-up, 16 out of 61 isolates were CRE-positive, with a prevalence of 26.23% per isolate and 16 out of 54 patients were positive, leading to 29.63% per patient. The total CRE prevalence, according to genotypic screening, was 10.23% per isolate (22/215) and 21.57% per patient (22/102). (Table 4)

The Test Result of CRE in phenotypic vs. genotypic (Vitek and RT-PCR/Xpert Carba-R) and genotypic vs. genotypic (RT-PCR vs Xpert Carba-R)

A phenotypic examination of CR microorganisms was performed using the Vitek method, while a genotypic examination was conducted with the Xpert Carba-R Molecular Test. The results from these two methods showed differences. The Vitek method identified 27 positive CR cases (26.47%) among the subjects, while the Xpert Carba-R Molecular Test detected 22 positive cases (21.57%). Additionally, 75 subjects (73.53%) tested CR-negative by the Vitek method, meanwhile 80 subjects (78.43%) tested negative using the Xpert Carba-R Molecular Test out of total 102 patients.

No.	Microorganisms Screened During Admission	CR+	CR-	Total (n = 161)
1	Escherichia coli	1	117	118 (73,29)
2	Klebsiella pneumoniae ssp pneumoniae	5	23	28 (17,39)
3	Enterobacter cloacae complex	2	-	2 (1,24)
4	Acinetobacter baumannii	1	-	1 (0,62)
5	Citrobacter amalonaticus	-	1	1 (0,62)
6	Citrobacter koseri	-	1	1 (0,62)
7	Comamonas testosteroni	-	1	1 (0,62)
8	Escherichia fergusonii	-	1	1 (0,62)
9	Morganella morganii ssp morganii	-	1	1 (0,62)
10	Negative	-	-	7 (4,35)
No	Microorganisms Screened During Follow-up	CR+	CR-	Total (n = 69)
1	Escherichia coli	0	30	30 (43,48)
2	Klebsiella pneumoniae ssp pneumoniae	16	9	25 (36,23)
3	Pseudomonas aeruginosa	2	-	2 (2,90)
4	Comamonas testosteroni	-	1	1 (1,45)
5	Enterobacter cloacae complex	-	1	1 (1,45)
6	Morganella morganii ssp morganii	-	1	1 (1,45)
7	Proteus mirabilis	-	1	1 (1,45)
8	Negative	-	-	8 (11,59)

Table 3. Prevalence of Microorganisms in the ICU Patients.

No.	Microorganisms Screened During Admission	CRE+	CRE-	Total (n = 161)
1	Escherichia coli	1	117	118 (73,29)
2	Klebsiella pneumoniae ssp pneumoniae	5	23	28 (17,39)
3	Enterobacter cloacae complex	-	2	2 (1,24)
4	Acinetobacter baumannii	-	1	1 (0,62)
5	Citrobacter amalonaticus	-	1	1 (0,62)
6	Citrobacter koseri	-	1	1 (0,62)
7	Comamonas testosteroni	-	1	1 (0,62)
8	Escherichia fergusonii	-	1	1 (0,62)
9	Morganella morganii ssp morganii	-	1	1 (0,62)
10	Negative	-	-	7 (4,35)
No	Microorganisms Screened During Follow-up	CRE+	CRE-	Total (n = 69)
1	Escherichia coli	0	30	30 (43,48)
2	Klebsiella pneumoniae ssp pneumoniae	16	9	25 (36,23)
3	Pseudomonas aeruginosa	-	2	2 (2,90)
4	Comamonas testosteroni	-	1	1 (1,45)
5	Enterobacter cloacae complex	-	1	1 (1,45)
6	Morganella morganii ssp morganii	-	1	1 (1,45)
7	Proteus mirabilis	-	1	1 (1,45)
8	Negative	-	-	8 (11,59)

 Table 4. Distribution of Carbapenem-Resistant Enterobacterales (CRE) by Genotypic Characteristics in ICU Patients at RSUPNCM

There was a similarity in the results between the genotypic examination of carbapenem-resistant organisms using Real-Time PCR and Rapid Molecular Test (Xpert-Carba R). Specifically, five subjects were found to have the NDM gene in *Klebsiella pneumoniae*, 16 subjects had the OXA-48 gene in *Klebsiella pneumoniae*, and one subject had the NDM gene in *Escherichia coli*.

However, there were differences between the results of CR organism testing with Xpert Carba-R and Vitek. The Vitek method detected 27 positive CR results, while Xpert Carba-R identified 22 positive CR results. For negative results, Vitek identified 75 CR-negative results, while Xpert Carba-R identified 80 CR-negative results. The sensitivity of Xpert Carba-R compared to Vitek was 81.48%, with a specificity of 100%. Theoverall accuracy of Xpert Carba-R compared to Vitek was 95.1%.

The Xpert Carba-R molecular rapid test demonstrated identical results to real-time PCR in diagnosing Carbapenem Resistant *Enterobacterales*. Thus, the sensitivity, specificity, positive predictive value, and negative predictive value, and accuracy of Xpert Carba-R were all 100%, with a case prevalence of 21.6%.

Discussion

In this study, the Cepheid Xpert[®] Carba-R rapid molecular test was compared with Real-Time PCR for detecting carbapenem resistance genes in CRE. Both methods targeted five specific carbapenem resistance genes: KPC, NDM, OXA-48, VIM, and IMP, which are commonly associated with resistance in Enterobacterales.⁸ Among the resistance genes identified, OXA-48 and NDM were the most prevalent, with 16 patients testing positive for OXA-48 and six for NDM. The majority of these resistance genes were detected during the second examination, suggesting that ICU-acquired CRE may have contributed to the increase in positive results. Other resistance genes, such as IMP and VIM, were not found in this study, though they have been

Table 5. Comparison of the Xpert Carba-Rand Vitek Test Results in DiagnosingCarbapenem Resistant (CR)

Assay		Vitek		
		Positive	Negative	
Xpert Carba-R	Positive	22	0	
	Negative	5	75	

Table 6. Diagnostic Value of Xpert Carba-R
Compared to Real-Time PCR in
Diagnosing Carbapenem Resistant-
Enterobacterales.

Assay		RT-	Nilai p	
		Positive	Negative	- Milai p
Xpert	Positif	22 (A)	0 (B)	<0,001
Carba-R	Negatif	0 (C)	80 (D)	

Sn	100%
Sp	100%
PPV	100%
NPV	100%
Prevalence	21,6%
Acc	100%

Fisher Exact Test

reported in other studies from Indonesia. Additionally, KPC, a resistance gene found in other regions, has never been documented in Indonesia, further supporting its absence in this study.^{3,9,10}

A key observation was that the Xpert Carba-R and RT-PCR results were consistent for the same isolates. However, a discrepancy observed between the culture-based phenotypic method (Vitek) and the molecular tests. Some carbapenem-resistant isolates detected by Vitek did not show resistance genes in either Xpert Carba-R or Real-Time PCR. This suggests that resistance in those isolates could be due to mechanisms or genes not covered by the five tested genes, highlighting the limitations of targeted molecular diagnostics.

In terms of bacterial species, *Klebsiel-la pneumoniae* and *Escherichia coli* were the dominant isolates. OXA-48 and NDM were the primary resistance genes in *K. pneumoniae*, while *E. coli* primarily harbored the NDM gene. This differs from previous study which found NDM to be the most prevalent gene in *K. pneumoniae*.³ However, the results are consistent with Hasibuan et al.¹¹, who reported a dominance of OXA-48 in K. pneumoniae isolates in Medan, Indonesia. Similarly, the dominance of the NDM gene in E. coli aligns with Govindaswamy et al.'s¹² results in India.¹

Previous studies observed NDM, KPC, VIM, IMP, and OXA-48 as the resistance genes observed in *Enterobacter cloacae complex* bacteria.¹³⁻¹⁸ Despite testing two *Enterobacter cloacae* isolates, no resistance genes were detected. This suggest that the carbapenem resistance in these isolates is due to other mechanisms not tested in this study. Future investigations using more comprehensive approaches, such as WGS, could help identify other resistance mechanisms.

According to the study by Saharman YR et al,³ the most dominant resistance gene in *Acinetobacter baumannii* bacteria is OXA-23, accounting for 292/318 (91.8%). Similarly, in the study by Anggraini D et al,⁹ the most common resistance genes in *Acinetobacter baumannii* in cases of systemic blood infection were OXA-51, OXA-23, and OXA-24, which may explain the absence of resistance genes detected by Xpert Carba-R or Real-Time PCR in this study.³

This is different from the results obtained in *Pseudomonas aeruginosa* bacteria, where the most dominant resistance genes according to Saharman YR et al,³ are VIM, IMP, and GES-5. Unfortunately, in this trial, none of these resistance genes were detected. This may be due to the fact that there were only a few isolates of *Pseudomonas aeruginosa* found, 2 out of 215 isolates, and these two isolates may not contain resistance genes VIM and IMP that are present in Xpert Carba-R or Real-Time PCR but contain other resistance genes such as GES-5.³

The diagnostic accuracy of the Xpert Carba-R in comparison with Real-Time PCR was excellent, with both tests showing 100% sensitivity, specificity, PPV, and NPV. This result aligns with other studies, such as Park et al.¹⁹, which reported high sensitivity (95.0%) and specificity (98.1%) for the Xpert Carba-R test.

These findings indicate that Xpert Carba-R can be a valuable tool for the rapid identification of CRE in clinical settings, especially in ICUs, where timely detection is crucial for preventing the spread of resistant organisms.

This study is limited by the fact that the Xpert Carba-R test only targets five carbapenem resistance genes (KPC, NDM, OXA-48, VIM, IMP). Other resistance mechanisms or genes may not have been detected, leading to some discrepancy between phenotypic and genotypic results. Further research using more comprehensive molecular techniques, such as WGS, may be needed to provide a complete picture of carbapenem resistance mechanisms.

Conclusion

The Xpert Carba-R molecular rapid test proved to be a reliable alternative for detecting carbapenem resistance genes, demonstrating perfect sensitivity, specificity, PPV, and NPV compared to Real-Time PCR. The method is particularly valuable for rapid screening in ICU settings, where early detection of CRE is important for infection control. Our study observed that *Escherichia coli* (68.8%) and *Klebsiella pneumoniae* (24.7%) were the most common CRE isolates, with OXA-48 (72.7%) and NDM (27.3%) being the dominant resistance genes found. This study indicates the importance of continuous surveillance and the potential benefit of molecular diagnostic tools in managing the spread of CRE in healthcare settings.

Declarations

Ethics and Regulatory Considerations

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia, approved the research on 18th October 2021 (No: KET 1013/UN2.F1/ETIK/PPM.00.02).

Consent for Participation

Informed consent was documented using a written consent form approved by the Ethics Committee Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital.

Availability of Data and Material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

All authors report no conflict of interest relevant to this article.

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