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RESEARCH

**ERROR RATE OF DISC DIFFUSION METHOD IN CEFTAZIDIME/
CEFOTAXIME SUSCEPTIBILITY TEST ON CLINICAL ISOLATES OF
KLEBSIELLA PNEUMONIAE**

(Laju Kesalahan Uji Kepekaan Ceftazidim/Cefotaxime Metode Difusi Cakram pada Klebsiella pneumoniae)

Luz Maria GBW, Osman Sianipar, Usi Sukorini

ABSTRAK

Klebsiella pneumoniae merupakan salah satu bakteri Gram negatif yang banyak menimbulkan infeksi nosokomial. Difusi cakram merupakan satu metode uji kepekaan antimikrobia yang banyak digunakan di laboratorium klinik yang juga dapat dipakai untuk menyaring *K.pneumoniae* penghasil enzim Extended-Spectrum β -Lactamase (ESBL). Antimikrobia pilihan untuk infeksi ini adalah cephalosporin generasi ketiga (ceftazidime dan cefotaxime). Penelitian ini bertujuan untuk mengetahui laju kesalahan uji kepekaan ceftazidime/cefotaxime metode difusi cakram di isolat klinis *K.pneumoniae*. Penelitian ini merupakan kajian potong lintang yang melibatkan 53 isolat klinis *K.pneumoniae*. Uji kepekaan ceftazidime/cefotaxime di isolat klinis *K.pneumoniae* dilakukan menggunakan metode difusi cakram dan uji E sebagai rujukan. Hasil pemeriksaan dilaporkan dalam bentuk kepekaan, intermediate dan resistensi untuk setiap obat, dianalisis untuk mengetahui laju kesalahan (minor error, major error dan very major error). Isolat klinis terbanyak berasal dari darah, air kemih dan nanah, berturut-turut 32,1%, 32,1% dan 18,9%. Sebagian besar isolat didapat dari ruang perawatan non-intensif (86,8%). Minor error uji kepekaan ceftazidime/cefotaxime metode difusi cakram berturut-turut 7,55% dan 1,89%, sehingga dapat disimpulkan bahwa metode difusi cakram uji kepekaan ceftazidime/cefotaxime dapat digunakan dalam uji kepekaan terhadap isolat klinis *K.pneumoniae*.

Kata kunci: Error rate, difusi cakram, ceftazidime/cefotaxime, *Klebsiella pneumoniae*

ABSTRACT

Klebsiella pneumoniae is one of Gram-negative bacteria causing hospital acquired infections. Disc diffusion as a method of antimicrobial susceptibility test the widely used in clinical laboratories and also can be used to screen Extended-Spectrum β -Lactamase (ESBL) producing *K.pneumoniae*. The third-generation of cephalosporin (ceftazidime/cefotaxime) are antibiotics commonly used for these infections. Therefore, this research aimed to know error rate of disc diffusion method in ceftazidime/cefotaxime susceptibility test on clinical isolates of *K.pneumoniae*. This research was carried out using cross-sectional method involving fifty-three clinical isolates of *K.pneumoniae*. Ceftazidime/cefotaxime susceptibility test on clinical isolates of *K.pneumoniae* was conducted using disc diffusion and E test as the reference methods. The test results were reported by classifying each drug into sensitive, intermediate, or resistant character and then analyzed and calculated for its value of error rate (minor error and very major error). The clinical isolates were mostly derived from blood, urine and pus, respectively 32.1%, 32.1% and 18.9%. Most isolates were isolated from non intensive care room (86.8%). Minor errors of ceftazidime/cefotaxime susceptibility tests using disc diffusion method were respectively 7.55% and 1.89%. Therefore, it can be concluded that the disc diffusion method can be used in ceftazidime/cefotaxime susceptibility tests as a method of antibiotic susceptibility test for clinical isolates of *K.pneumoniae*.

Key words: Error rate, disc diffusion, ceftazidime/cefotaxime, *Klebsiella pneumoniae*

INTRODUCTION

Klebsiella pneumoniae is one of the Gram-negative bacteria causing nosocomial infections leading to morbidity and death.¹ Based on the data from *National*

Nosocomial Infection Surveillance (NNIs) from 1986 to 2003, there are four (4) types of *hospital-acquired infections* caused by epidemiological Gram-negative bacteria mostly found in the Intensive Care Unit (ICU). They are pneumonia, infection in surgical site, urinary

tract infections and blood stream. The bacteria mostly causing diseases associated with the above conditions are dominated by Gram-negative bacteria, one of which is *Klebsiella pneumoniae*.²

Based on a research conducted in the ICU of Dr. Wahidin Sudirohusodo Hospital in Makassar in 2009, moreover, *K.pneumoniae* which was the bacteria mostly found, about 28.3%.³ Based on the data of bacteria pattern derived from the Dr. Sardjito Hospital, *K.pneumoniae* is a bacteria always categorized into the top 10 types of bacterias. For instance, based on the data of inpatient in the second half of 2014, *K.pneumoniae* was the fourth bacteria mostly found after *Streptococcus viridans*, *Escherichia coli* and *Pseudomonas aeruginosa*. Besides that, 6.1% of *K.pneumoniae* derived from ICU patients in the US hospitals from January 1998 to June 2002 played a role in the *National Nosocomial Infection Surveillance* (NNIS) system, but they were not sensitive to the third generation of cephalosporin or aztreonam.⁴

The third-generation of Cephalosporin (ceftazidime and cefotaxime), furthermore, has been used extensively in the treatment of various infectious diseases because it has stronger and broader activities than the previous generations against Gram-negative bacteria.⁵ The wide and long use of cephalosporin as the third-generation can cause resistance of bacteria. For instance, it can cause displacement of β -lactamase resulting in its increased activity and hydrolyze the third generation of cephalosporin and aztreonam referred to Extended-Spectrum β -Lactamase (ESBL). The third-generation of cephalosporin marketed in the 1980s has caused smaller nephrotoxic impacts than aminoglycosides and polymyxin. Consequently, cephalosporin has been mostly and widely used. The wide use of cephalosporin can lead to the resistance of *K.pneumoniae*, so susceptibility test of ceftazidime and cefotaxime as antibiotics is necessary.⁶

In addition, the results of in vitro susceptibility test can guide clinicians to select early empiric regimen and special drugs. The easy way is by using disc diffusion method. This method is still widely used in clinical laboratories because the process is fast, easy and inexpensive, as well as can test several antibiotics at the same time. This method can also become a filter for *K.pneumoniae* as ESBL enzyme producer.⁷

In interpreting and reporting the results of susceptibility test on bacteria, there are possibilities of error. Based on the impact of errors in the treatment of patients, errors can be classified into minor one, major and very major. Such errors can be detected by compared examination method of bacteria susceptibility test with reference method.⁷

Minor errors (mE) are defined when bacteria are considered to be *intermediate* by using reference method or test. Whereas by using other methods they are considered to be resistant or sensitive. Major Errors (ME) are defined if the bacteria are considered to be sensitive by using reference method, but they are considered to be resistant by using susceptibility test method. Very Major Errors (VME) are defined when the bacteria are considered to be resistant by using reference method, but they are considered to be sensitive by using susceptibility test method. The value that is not acceptable for VME is less than 1.5%. The value that is not acceptable for ME is more than 3%, while value that is not acceptable for mE is more than 10% as recommended in CLSI data records, M23-A2.⁸ Major errors and the very (major errors) respectively describe fake resistance and sensitivity.⁹

There are some impacts of minor errors in interpreting results of the susceptibility test in patients using the vileded method with the result of the test as intermediary. Meanwhile, with the reference method, susceptibility may not be too large because drugs still can inhibit the growth of bacteria. However, if by using the reference method they are considered to be resistant, drugs given to the patients will not be able to inhibit the growth of bacteria and may make the patients can not be recover and the drugs given not useful.

In addition, there are also some impacts of major errors. For instance, patients who do not get drugs that should be given, so the growth of bacteria cannot be inhibited or better given another drug, higher class and more expensive one, without triggering organ damage. The very major error is caused by inappropriate drugs given to patients will not give any effect in inhibiting the growth of bacteria, so the disease will not be cured and can lead to more severe condition. Thus, the errors can lead to death since the infection is not resolved, and the costs are more expensive due to longer care. Mortality due to a mismatch between susceptibility of germs and treatment given to patients was ranged from 50 to 100%.¹⁰

Finally, based on the impacts of errors described above, the error rate of disc diffusion method in susceptibility test of the third-generation of cephalosporin (ceftazidime and cefotaxime) is needed to be analyzed, so the impact of major errors and very (major errors) can be avoided and the quality of antibiotic susceptibility test service can be guaranteed. Therefore, this research aimed to know the error rate (minor errors, major errors and very major errors) of disc diffusion method in ceftazidime/cefotaxime susceptibility tests on clinical isolates of *K.pneumoniae* determination of the study.

METHODS

This research was an analytical observational research with cross-sectional design. This research aimed to know the error rate of ceftazidime and cefotaxime susceptibility tests on clinical *K.pneumoniae* isolates determine of the study. The subjects were detected *K.pneumoniae* isolates examined by using automated tools in the Clinical Laboratory Installation of Dr. Sardjito Hospital with complete data about the subjects' characteristics. In this research, there was no participatory standard. Based on the valuation formula, sample size for comparison of specific populations and large minor errors that are acceptable under the guidelines of <10%, obtained a sample size of this study of 35 isolates.

The examination was then conducted using disc diffusion method. First, the discs of ceftazidime/cefotaxime were put onto Mueller Hinton agar surface inoculated clinical isolates of *K.pneumoniae*. Second, they were then incubated for 16–18 hours. Third, the diameter of inhibitory area was measured and reported in the form of sensitive, intermediate and resistant condition. Fourth, an examination using E test was conducted. During the examination, strips E of ceftazidime/cefotaxime were put in petri of Mueller Hinton agar which was already inoculated with suspension of *K.pneumoniae* isolates based on McFarland codification of 0.5. Each strip consisted of an antibiotic gradient already set, which allowed for the measurement of MIC in the range of 0.25 to 16 mg/mL for cefotaxime strip and 0.5 to 32 mg/mL for ceftazidime strip.

Next, the results of further examination were reported by classifying every antibiotic into sensitive, intermediate, or resistant character and then analyzed to determine the rate of errors (minor errors, major errors and very major errors). Finally, this research had been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, University of Gadjah Mada.

RESULTS AND DISCUSSION

Quality control of internal examination of the disc diffusion was conducted in the form of sterility test on the media and controlling factors affecting the examination, ie, media (pH, thickness, moisture), inoculum and incubation time. Moreover, the regional interpretation of resistancy (sensitive, intermediate and resistant) were performed by two (2) observers. Consequently, the Kappa test was required to establish confidence in reading the results of CDT method. Kappa index of resistance area reading either using ceftazidime or cefotaxime was about 0.97. The Kappa index value above indicated the strength of a good deal.

Furthermore, the total samples was 53 isolates. The characteristics of the samples are descriptively shown in Table 1. The age of the isolate sources mostly found was more than 55 years old. The largest samples found in this research were blood (32.1%) and urine (32.1%).

The research conducted by Sarojamma *et al*¹¹ on the prevalence of ESBL-producing *K.pneumoniae* in the third hospital reported that most samples obtained were blood, feces, sputum, urine and pus.¹¹

On the other hand, this research showed that 13.2% of the patients were treated in emergency room. *Klebsiella pneumoniae* is an important factor triggering infections found in the hospitals, particularly neonatal patients in *Intensive Care Unit* (ICU) with mortality rate up to 70%. *Intensive Care Unit* is one of transmission sources of *Klebsiella sp* bacteria due to several factors, such as severity level of disease, length of hospitalization, painful medical equipment and long antibiotic use.¹² In the last two (2) decades, the prevalence of infections caused by *multidrug-resistant K.pneumoniae* strain has reportedly increased.¹³ According to Warganegara and Apriliana⁵, infections caused by ESBL-producing bacteria can lead to prolongation of the use of antibiotics and the length of stay in ICU, as well as it can aggravate the disease causing the requirement of painful medical instruments.

In ceftazidime susceptibility test on *K.pneumoniae* isolates using disc diffusion method, there were four (4) isolates considered to be intermediate, but become resistant using E test (see Table 2).

In cefotaxime susceptibility test using disc diffusion method, there was one (1) isolate considered to be

Table 1. The characteristics of *K.pneumoniae* isolate sources

Characteristics of subjects	N	%
Number of research subjects	53	100
Age*		
Toddlers (0–5 years old)	14	28
Kids (>5–18 years old)	3	6
Adults (>18–55 years old)	14	28
Elderly (>55 years old)	19	38
Source of samples		
Blood	17	32.1
Pus	10	18.9
Urine	17	32.1
Feces	3	5.7
Sputum	1	1.9
LCS	1	1.9
Others	4	7.5
Room of treatment		
Emergency room	7	13.2
Non-emergency room	46	86.8
Types of treatment		
Surgery	15	28.3
Non-surgery	38	71.7

* Source: the Ministry of Health in 2009

Table 2. Interpretation of the ceftazidime antibiotic susceptibility test using disc diffusion method

	Classification	E Test			Total
		Sensitive	Intermediate	Resistant	
Disc diffusion	Sensitive	4	-	-	4
	Intermediate	-	-	4	4
	Resistant	-	-	45	45
Total		4	0	49	53

Table 3. Interpretation of cefotaxime antibiotic susceptibility test using disc diffusion method

	Classification	E Test			Total
		Sensitive	Intermediate	Resistant	
Disc diffusion	Sensitive	4	-	-	4
	Intermediate	-	-	1	1
	Resistant	-	-	48	48
Total		4	0	49	53

intermediate, but become resistant using E test (see Table 3).

Errors obtained in ceftazidime susceptibility test on *K.pneumoniae* isolates using disc diffusion method were minor errors about 7.55% (95% CI: 7.48–7.62%), but there was no major errors and the very major errors. Meanwhile, errors obtained in cefotaxime susceptibility test were minor errors about 1.89% (95% CI: -1.81–5.53%). There were no major errors and the very major errors in both antibiotic susceptibility tests (0%). The rate of minor errors still acceptable were less than 10%. The results of the above error rate indicated that minor error rate found in both ceftazidime and cefotaxime susceptibility tests using disc diffusion method were still acceptable.

CONCLUSION

In conclusion, ceftazidime susceptibility test on clinical isolates of *K.pneumoniae* had a minor error of 7.55%, a major error of 0% and the very major error of 0%. On the other hand, cefotaxime susceptibility test on clinical isolates of *K.pneumoniae* had a minor error of 1.89%, the major error of 0% and the very major error of 0%. Therefore, disc diffusion method can be used in ceftazidime/cefotaxime susceptibility test on clinical isolates of *K.pneumoniae*. For these reasons, research on error rate of antibiotic susceptibility test using disc diffusion method is expected to be continued by using other classes of antibiotics, such as the fourth-generation of cephalosporins, fluoroquinolones and carbapenem.

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