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# Comparison of Carbapenem Resistance Detected by the BD Phoenix Automated System in Enterobacteriaceae Isolates with E-Test Method

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| ARTICLE INFO | ABSTRACT |
|---|---|
| | **Objective:** Automatic identification and antimicrobial susceptibility systems are frequently used to identify clinical isolates in hospitalized patients, but mistakes in these systems can lead to potentially devastating treatment failures for patients. Therefore, the ''Centers for Disease Control and Prevention (CDC)'' recommends confirming all Carbapenem-resistant and low-susceptibility isolates with a different method. The aim of this study is to compare the Carbapenem susceptibility results of isolates reported as Carbapenem-resistant *Enterobacteriaceae* according to the BD Phoenix 100 automated system with the E-test method.<br><br>**Materials and Methods:** The study included 70 strains of Carbapenem-resistant *Enterobacteriaceae* members which were isolated and grown from several types of clinical samples in the Medical Microbiology Laboratory. Conventional methods (Gram stain, negative oxidase test) and the BD Phoenix 100 automated system were used to identify the isolates. The susceptibility of all strains to imipenem, ertapenem and meropenem was investigated by E-test method. Automated system results and E-test results were compared.<br><br>**Results:** The frequency distribution of all isolated bacterial strains comprised *K. pneumoniae* in 56 (80%) of the samples included in the study. The automated system test results were correlated with the results of the E-test at a rate of 96.1 % for the imipenem-resistant strains, 84.3% for the meropenem-resistant strains, 84.1% for the ertapenem-resistant strains<br><br>**Conclusions:** Automated systems are frequently used in microbiology laboratories to identify isolates. However, automated systems can show a high error rate against some antimicrobials. For this reason, comparing the results of automated system test results with tests such as E-test is very important to prevent both treatment failures and inappropriate antibiotic use that may occur on a patient basis.<br><br>**Keywords:** Enterobacteriaceae, e-test, Carbapenemase |

## INTRODUCTION

*Enterobacteriaceae* is a bacteria family containing a large number of genera and species, which are often isolated as infectious agents from humans [1]. The main pathogens in this group include *Escherichia, Klebsiella, Citrobacter, Enterobacter, Proteus, Providencia, Serratia, Hafnia, Morganella, Edwardsiella, Yersinia, Shigella*, and *Salmonella* [2]. The rates of antimicrobial resistance have significantly increased in hospitalized patients in recent years [3]. Resistance mechanisms against Carbapenems basically involve β-lactamase production, and mutations altering the expression and/or functions of efflux pumps, porins, and penicillin-binding proteins (PBP) [4]. Carbapenem-hydrolyzing β-

lactamases (Carbapenemases) are the most potent, capable of hydrolyzing almost all β-lactams. Their worldwide spread among the members of the *Enterobacteriaceae* family creates a major concern [5]. Treatment options are limited and mortality rates are high in patients with infections, in which Carbapenem-resistant *Enterobacteriaceae* (CRE) are the causative agents [6]. In addition, the properties of the tested antibiotic also affect the susceptibility test results. For example, imipenem is easily degraded due to its instability. Although meropenem is more stable than imipenem, susceptibility panels, disc monitoring and storage conditions are required for both antimicrobials. Therefore, the ''Centers for Disease Control and Prevention (CDC)'' recommends confirming all Carbapenem-resistant and low-susceptibility isolates with a different method [7]. E-test (Epsilometer test)

method is an antifungal and antibacterial susceptibility assay, introduced in 1988 [8]. This test serves as an alternative option to the reference methods as it is practical, easily applicable and it can provide the test results earlier compared to other existing assays [9]. In this study, it was aimed to compare the Carbapenem susceptibility results of isolates sent from the patients followed in different clinics of our hospital to the laboratory and evaluated as CRE with the BD Phoenix 100 automated system as a result of culture, using the E-test method.

## MATERIALS AND METHODS

The isolates were obtained from clinical samples of the Van Yuzuncu Yil University Hospital Medical Microbiology Laboratory between August 2016 and August 2017, with minimal inhibitory concentration (MIC) value increase according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria against at least one of the imipenem, ertapenem and meropenem antibiotics with the BD Phoenix 100 (Sparks, MD, USA) automated system were included in the study. Conventional methods (Gram stain, negative oxidase test) and the BD Phoenix 100 automated system were used to identify the isolates. All of the isolates included in the study were isolated from patients hospitalized at different dates and in different clinical units, and only one clinical isolate was accepted from each patient. During the study period, 70 CRE strains satisfying these conditions were isolated and stored in glycerol broth storage medium at -80 °C. The susceptibility of all strains to imipenem, ertapenem and meropenem was investigated by E-test (Biomerioux, France) method. A 0.5 McFarland turbidity bacterial suspension was prepared from the isolates and inoculated on Müeller Hinton agar (RTA, Turkey) plate. E-test strips were placed on the agar surface and incubated for 16-20 hours. At the end of this period, MIC values were determined by evaluating the imipenem, ertapenem and meropenem E-test results of all strains. Automated system results and E-test results were compared.

Descriptive statistics for continuous variables; It was expressed as mean, standard deviation, minimum and maximum values, while for categorical variables it was expressed as numbers and percentages.

### Ethical Statement

Ethics committee approval dated 2016 and numbered B.30.2.YYU.0.01.00.00 was obtained from Van Yuzuncu Yil University, Faculty of Medicine Clinical Research Ethics Committee Presidency to carry out this study.

## RESULTS

When the bacterial isolates submitted to the Microbiology laboratory were evaluated for their distribution by the clinical departments, it was observed that 28 (40%) samples were found to be collected from the Anesthesia and Reanimation Intensive Care Unit (ICU), followed by the 12 (17.1%) samples collected from the Neurology ICU, 7 (10%) from the Internal Medicine ICU, and 5 (7.1%) from General Surgery ICU, respectively (**Table 1**).

The frequency distribution of all isolated bacterial strains comprised *Klebsiella pneumoniae* in 56 (80%) of the samples

**Table 1.** Distribution of clinical isolates by service/polyclinics

| Clinics | No. of isolates | % |
|---|---|---|
| Anesthesia and reanimation ICU | 28 | 40 |
| Neurology ICU | 12 | 17.1 |
| Internal medicine ICU | 7 | 10 |
| General surgery ICU | 5 | 7.1 |
| Urology polyclinic | 4 | 5.7 |
| General surgery service | 3 | 4.3 |
| Orthopedics and traumatology service | 3 | 4.3 |
| Infectious diseases service | 2 | 2.9 |
| Chest diseases service | 2 | 2.9 |
| Urology service | 2 | 2.9 |
| Coronary ICU | 1 | 1.4 |
| Oncology service | 1 | 1.4 |

**Table 2.** Carbapenem-resistant *Enterobacteriaceae* (CRE) distribution

| Species | No. of isolates | % |
|---|---|---|
| *K.pneumonia* | 56 | 80 |
| *E.coli* | 10 | 14.3 |
| *P.mirabilis* | 1 | 1.4 |
| *E.cloacae* | 2 | 2.9 |
| *P.agglomerans* | 1 | 1.4 |

**Table 3.** Clinical samples submitted to the laboratory

| Clinical samples | No. of isolates | % |
|---|---|---|
| Urine | 22 | 31.4 |
| Tracheal aspirate | 18 | 25.7 |
| Blood | 13 | 18.6 |
| Wound | 8 | 11.4 |
| Sputum | 4 | 5.7 |
| Catheter | 4 | 5.7 |
| Abscess | 1 | 1.4 |

**Table 4.** Resistance rates on the Phoenix BD and E-test method

| Test method | Antibiotic resistance | | | Total number of strains |
|---|---|---|---|---|
| | Imipenem | Ertapenem | Meropenem | |
| Phoenix BD | 26 (37.1%) | 69 (98.6%) | 35 (50%) | 70 |
| E-test | 25 (36%) | 58 (83%) | 32 (46%) | 70 |

included in the study, followed by *Escherichia coli* in 10 (14.3%) and *Enterobacter* in 2 (2.9%) samples. All of the isolated strains are given in **Table 2**.

In the distribution of clinical samples, the majority of the samples are urine (n=22, 31.4%), tracheal aspirate (n=18, 25.7%), blood (n=13, 18.6%) samples, respectively. Distributions of clinical sample types are given in **Table 3**.

Of the 70 isolates tested in the automated system, the highest rate of resistance was observed with the ertapenem (69 isolates, 98.6%) among the studied Carbapenems. Resistance to meropenem and imipenem was observed in 35 isolates (50%) and 26 isolates (37.1%) respectively. The E-test results revealed resistance rates of 83% (58 isolates) to ertapenem, 36% (25 isolates) to imipenem, 46% (32 isolates) to meropenem. The resistance rates found by the automated system and the E-test method are given in **Table 4**.

## DISCUSSION

This study was carried out to perform E-test on *Enterobacteriaceae* isolates with Carbapenem resistance detected in the automated system and to compare the two test

methods. *K. pneumoniae* was the most common (80%) isolated in the study. According to both automated system and E-test results, the highest rate of resistance was observed against ertapenem (98.6% and 83%). The fact that the Carbapenem resistance rate was found to be lower according to the automated system result compared to the E-test method indicates that Carbapenem resistance correlation with a different test is required.

Resistance to antibiotics in bacteria has been on the rise in the last 30-40 years. Nowadays, bacterial infections with multiple resistance are a major critical concern of physicians and a life-threatening issue for the patients especially in intensive care units [10]. In infections caused by Carbapenem-resistant microorganisms; mortality and morbidity rates are high, hospital stays are longer, and treatment costs are increased. Furthermore, these infections are of critical importance because the world is running out of effective antibiotics, facing a rapid spread of resistance [11].

In the literature, the distribution of the types of samples, from which Gram-negative bacteria were isolated, is variable across studies. In 2011, the authors in [12] evaluated 1,346 *Enterobacteriaceae* strains isolated in 25 different microbiology laboratories from 23 different cities in Italy and reported that, of all the isolates, 48.6% were isolated from urine, 13.2% from blood, and 16.2% from the lower respiratory tract samples. Of 270 patients with Carbapenemase resistance, *K.pneumonia* growth was observed in 234 (86.7%) patients. Carbapenem-resistant *E.coli* ratio was found to be 0.06% . In a study conducted in Spain, *K.pneumoniae* was detected in 85% and *E. coli* in 1.7% in the bacterial isolates obtained from the patients with infections caused by Carbapenem-resistant enteric bacteria [13].

In a study conducted in Turkey, *K.pneumonia* was found in 70.5% and *E.coli* was found in 13.4% of the clinical isolates [14]. In another study conducted in Turkey, Carbapenem resistance was determined in 4.59% of *Enterobacteriaceae* family bacteria grown from various clinical specimens over a 3-year period, and the most frequently detected agent was *Klebsiella spp.* (71.43%) [15]. Similar to the previous studies in the literature, the most frequent rate of growth was observed for the urine culture samples (31.4%) in our study, too. This growth rate was followed by a rate of 25.7% for the tracheal aspirate cultures and 18.6% for the blood culture samples respectively. In regards to the bacterial growth, the growth of *K.pneumoniae* and *E.coli* were observed at a rate of 80% and 14.3%, respectively. It was observed that *K.pneumoniae* was isolated more frequently similar to the previous studies in the literature.

Patients admitted to intensive care units (ICUs) are individuals often undergoing invasive interventions, receiving broad-spectrum antibiotics, and staying at the hospital for longer periods due to poor general condition compared to the other groups of patients [16]. In a study conducted in Italy [12], it was observed that 42.5% of the patients with Carbapenem-resistant *Klebsiella* growth were inpatients in ICU. In a study in Mumbai [17], 12% of Carbapenem-resistant enteric bacteria were isolated from patients in intensive care units. A study conducted in Turkey observed that 42.9% of the isolates in the laboratory were prepared from clinical samples taken from ICU patients and they were mostly collected in Anesthesia and Reanimation ICU at a rate of %26 [18]. Similar to other studies, it was observed that the isolates were most commonly submitted by ICU's (72.8%) in our study. The frequency distribution of ICUs revealed that the isolates were most commonly submitted by the Anesthesia and Reanimation ICU (40%).

Many laboratories use automated identification and antimicrobial susceptibility systems to identify clinical isolates to save time, especially in hospitalized patients. Mistakes in these systems can lead to potentially devastating treatment failures for patients with CRE-related infections. Because of the significant morbidity and mortality caused by CRE-associated infections, it is very important for physicians to evaluate which drugs are the most appropriate option to treat these infections [19]. The Phoenix TM Automated Microbiological System is a system that provides rapid species-level bacterial identification and antibiotic susceptibility results of clinically important human bacterial pathogens. In addition, this automated system allows the identification of isolates with resistance mechanisms, including extended spectrum-lactamases (ESBL), acquired AmpC, and the identification of specific Carbapenemases in Gram-negatives [20].

E-test MBL (Metallo-beta-lactamase) strip method is used for identifying MBL-producing isolates. The E-test is among the methods determining MIC and it is more commonly preferred because it is easier and more practical compared to agar dilution [21,22]. A study, comparing disk diffusion, broth microdilution, E-test, and automated systems to determine susceptibility to imipenem, meropenem, and ertapenem, reported the E-test sensitivity as 58-90%. This rate is higher, especially for ertapenem [23]. In a study which comparing the antibiotic susceptibility of bacteria isolated from urine culture with conventional methods and automated systems has shown that agreement for E-test was 95.3% with a very major error rate of 1.1 [24]. In a study comparing meropenem MICs and susceptibility with various tests in Carbapenem-resistant *K. pneumonia* strains; E-test demonstrated 82.6% agreement with broth microdilution MICs, a very major error rate of 2.2%, and a minor error rate of 2.2% and Vitek 2 automated system MIC agreement was 30.4%, with a 23.9% very major error rate and a 39.1% minor error rate [25].

Another study in which ertapenem resistance in the *Enterobacteriaceae* family was compared with different antimicrobial susceptibility tests and the broth microdilution test was used as the reference test, E-test showed high sensitivity and specificity (85.0% and 88.5%, respectively) and excellent concordance with BMD and the VITEK2 showed the lowest essential and categorical agreement (30.5% and 27.8%, respectively) [26]. It was observed that a resistance rate of 97.7 % to ertapenem was detected using antimicrobial gradient test techniques, whereas the resistance rate was 100 % according to the VITEK®2 automated system [27]. Additionally, meropenem resistance was calculated using the antimicrobial gradient test (93 %) and the automated system (90.7 %).

In another study [28], metallo-b-lactamase (MBL) producing strains and Carbapenem resistance *K. pneumoniae* isolates were compared in terms of Carbapenem susceptibility with Vitek-2 and Phoenix automated systems and E-test methods. Phoenix showed higher categorical agreement (97% for imipenem and 94% for meropenem) compared to Vitek-2 (92% vs. 74%) and E-test (89% vs. 96%) in detecting MBL strains. Categorical agreement for imipenem in detecting KPC producing strains was 88.4% with the Phoenix system, 83.2% with the Vitek 2 system, and 90.5% with the E-test. Also, categorical agreement was 100% for all tests with Ertapenem.

In this study the highest rate of resistance was observed with the ertapenem (98.6%) among the studied Carbapenems

(resistance to meropenem and imipenem 50% and 37.1% respectively) according to the automated system. The E-test results revealed resistance rates of 83% to ertapenem, 36% to imipenem, 46% to meropenem. When E-test and automated system are compared; while the sensitivity rate of imipenem was similar in both tests, ertapenem and meropenem results were found to be lower in the E-test method. Although automated systems provide very important conveniences especially for hospitalized patients, erroneous results of the test can create a serious problem. The result of the automated system should be compared and verified with a different test under appropriate conditions.

## CONCLUSIONS

In our country, Carbapenem-resistant *Enterobacteriaceae*-related infections have increased significantly in recent years. In this study, it is seen that the most frequently isolated bacteria in the family of Carbapenem-resistant *Enterobacteriaceae* is *K.pneumonia* and the intensive care units is the hospital department where these resistant strains are most common. Although molecular methods are accepted as the gold standard in detecting Carbapenemases, they cannot be performed in every laboratory due to factors such as intensive labor, technical infrastructure and cost. Automated systems are frequently used in microbiology laboratories to identify isolates. However, automated systems can show a high error rate against some antimicrobials.

In this study, the rate of Carbapenem resistance was found to be higher than the E-test method according to the result of the automated system. For this reason, comparing the results of automated system test results with tests such as E-test is very important to prevent both treatment failures and inappropriate antibiotic use that may occur on a patient basis.

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