# Diagnosis and Management of Infections Caused by *Enterobacteriaceae* Producing Extended-Spectrum β-Lactamase

*Audrey Amelia, Agung Nugroho, Paul N. Harijanto*

Department of Internal Medicine, Faculty of Medicine, University of Sam Ratulangi - Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia.

***Corresponding Author:***
*Audrey Amelia, MD. Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, University of Sam Ratulangi - Prof. Dr. R. D. Kandou Hospital. Jl. Raya Tanawangko, Manado 95115, Indonesia. email: audrey_amelia@yahoo.com.au.*

## ABSTRAK

*Resistensi bakteri terhadap antibiotik merupakan salah satu masalah yang sangat serius di seluruh dunia yang berdampak pada meningkatnya angka morbiditas dan mortalitas, salah satunya adalah akibat Enterobacteriaceae penghasil ESBL. Meskipun demikian, informasi mengenai penegakan diagnosis dan penatalaksanaan infeksi ESBL-E masih terbatas. Deteksi ESBL-E memerlukan beberapa tahap yang cukup sulit dan memerlukan waktu yang lama. Diagnosis dan penatalaksanaan infeksi akibat ESBL-E menjadi semakin sulit karena keterbatasan metode diagnosis yang ada dan pilihan antibiotik yang dapat digunakan, bersamaan dengan subtipe ESBL yang terus berkembang melalui proses mutasi yang beragam. Artikel ini bertujuan untuk memberikan gambaran mengenai keadaan terkini tentang infeksi ESBL-E yang terfokus pada diagnosis dan penanganan infeksi tersebut melalui pembahasan beberasa studi mengenai masalah ini.*

***Kata kunci:*** *resisten multi obat, ESBL, diagnosis, penatalaksanaan.*

## ABSTRACT

*Bacterial resistance to antibiotics is a serious problem worldwide that affect the increment of morbidity and mortality rate; Enterobacteriaceae producing ESBL is one of the causes. However, there are still limited information regarding diagnosis and management of ESBL-E infection. Detection of ESBL-E requires certain steps that are problematic and time consuming. Diagnosis and management of ESBL-E infection have become more and more challenging due to limited diagnostic method available and choice of antibiotics that may be used, along with growing subtyped of ESBL through various of mutations. This article is aimed to give an overview on current situation of ESBL-E infections, with a focus on diagnosis and management of such infection by reviewing several recent studies on related issue.*

***Keywords:*** *multi-drug resistant, ESBL, diagnosis, management.*

## INTRODUCTION

Bacterial resistance to antibiotics is a serious problem worldwide. Until recently, many cases of resistance towards antibiotics are known due to methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococci* (VRE), penicillin-resistance *Pneumococci*, carbapenem-resistance *Acinetobacter baumanni*, multi-resistant *Mycobacterium tuberculosis*, and *Enterobacteriaceae* producing extended-spectrum β-lactamase (ESBL).[1]

Production of ESBL is an important mechanism causing resistance towards 3rd generation of cephalosporin, such as ceftazidime, ceftriaxone, and cefotaxime, which is commonly used, for empirical therapy of antibiotics. The growing prevalence of infection due to *Enterobacteriaceae* producing ESBL (ESBL-E) cause challenge in treating nosocomial infection that usually treated empirically with cephalosporin and fluoroquinolon. Delayed diagnosis and management are related to high mortality, hospital cost and length of stay in the hospital.[2,3]

Since more than 70% of world populations live in the Asia-Pacific region, antibiotic resistance in Asia is also considered as a global problem. The Study for Monitoring Antimicrobial Resistance Trends (SMART) which monitor the pattern of antibiotic resistance in intra-abdominal infection since 2002 and urinary tract infection since 2009 until 2011, found the main multi-resistant bacteria causing infection are *Escherichia coli* and *Klebsiella pneumoniae* with the prevalence of 47.8% and 14.5% respectively in intra-abdominal infection, whereas in urinary tract infection are 44.3% and 11.8% respectively. Moreover, the SMART study also obtained that highest prevalence of ESBL-E infection is in Asia, which is more than 40%, followed by Latin America and the Middle East. The SMART study also showed increasing pattern of infection by ESBL-E prevalence in Asia.[4,5]

The use of broad-spectrum antibiotics, especially third generation of cephalosporin and fluoroquinolon leads to the growth of ESBL-E in hospital and associated with high treatment failure and mortality. Early control of ESBL-E in sepsis patients due to nosocomial infection and adequate treatment is essential in patients' management.[2] This review will discuss about the diagnosis and management of ESBL.

## DEFINITION OF ESBL

Extended spectrum β-lactamase (ESBL) is an enzyme produced by certain bacteria causing them to become resistant to several antibiotics including third generation of cephalosporin and aztreonam. This enzyme works by hydrolyzing β-lactam ring in β-lactam antibiotics (BL). It is carried in the chromosomes of those particular bacteria and transferred to other populations of bacteria through plasmid. There are several ESBL-E known today, including *Klebsiella pneumoniae* (ESBL-KP) and *Escherichia coli* (ESBL-EC). The ESBL-E infection firstly found was an infection by *K. Pneumonia* in Germany in the year of 1983 and spread to all Europe as well as America. In Asia, the first infection was found in China in 1988.[6-8]

## CLASSIFICATION OF ENZYME B-LACTAMASE

There are many classification schemes available for enzyme β-lactamase, however the most commonly used are the Ambler classification and the Bush-Jacobsky classification. Ambler classification, was first communicated in 1991, categorized ESBL into 4 classes, that are A, B, C, and D based on their amino acid structure, where class A, C and D have an active side of serine-β-lactamase and class B have an active side of metallo-β-lactamase.[8,9]

The Bush-Jacobsky-Mendeiros was first introduced in 1989, expanded on 1995 and renewed to become Bush-Jacobsky classification in the year of 2009, where β-lactamase enzyme is categorized into 4 different groups, presented in **Table 1**. The first group is cephalosporinase or AmpC, also known as Ambler class C. It is more active towards cephalosporin compared to benzilpenicillin and usually resistant to clavulanate acid inhibition, also active towards cephamicin such as cephotixin, and high affinity toward aztreonam.[9]

The second group is also known as serine-β-lactamase. It is the largest group of β-lactamase

**Table 1.** Enzyme β-lactamase classification[9]

| Bush-Jacoby group (2009) | Bush-Jacoby-Medeiros group (1995) | Molecular class (subclass) | Distinctive substrate(s) | Inhibited by | | Defining characteristic(s) | Representative enzyme(s) |
|---|---|---|---|---|---|---|---|
| | | | | CA or TZB[a] | EDTA | | |
| 1 | 1 | C | Cephalosporins | No | No | Greater hydrolysis of cephalosporins than benzylpenicillin; hysrolyzes cephamycins | E.coli AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1 |
| 1e | NI[b] | C | Cephalosporins | No | No | Increased hydrolysis of ceftazidime and often other oxymino-β-lactams | GC1, CMY-37 |
| 2a | 2a | A | Penicillins | Yes | No | Greater hydrolysis of benzylpenicillin than cephalosporins | PC1 |
| 2b | 2b | A | Penicillins, early cephalosporins | Yes | No | Similar hydrolysis of benzylpenicillin and cephalosporins | TEM-1, TEM-2, SHV-1 |
| 2be | 2be | A | Extended-sepctrum cephalosporins, monobactams | Yes | No | Increased hydrolysis of oxymino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam) | TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1 |
| 2br | 2br | A | Penicillins | No | No | Resistance to clavulanic acid, sulbactam, and tazobactam | TEM-30, SHV-10 |
| 2ber | NI | A | Extended-spectrum cephalosporins, monobactams | No | No | Increased hydrolysis of oxymino-β-lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam | TEM-50 |
| 2c | 2c | A | Carbenicillin | Yes | No | Increased hydrolysis of carbenicillin | PSE-1, CARB-3 |
| 2ce | NI | A | Carbenicillin, cefepime | Yes | No | Increased hydrolysis of carbenicillin, cefepime, and cefpirone | RTG-4 |
| 2d | 2d | D | Cloxacillin | Variable | No | Increased hydrolysis of cloxacillin or oxacillin | OXA-1, OXA-10 |
| 2de | NI | D | Extended-spectrum cephalosporins | Variable | No | Hydrolyzes cloxacillin or oxacillin and oxymino-β-lactams | OXA-11, OXA-15 |
| 2df | NI | D | Carbapenems | Variable | No | Hydrolyzes cloxacillin or oxacillin and carbapenems | OXA-23, OXA-48 |
| 2e | 2e | A | Extended-spectrum cephalosporins | Yes | No | Hydrolyzes cephalosporins. Inhibited by clavulanic acid but not aztreonam | CepA |
| 2f | 2f | A | Carbapenems | Variable | No | Increased hydrolysis of carbapenems, oxymino-β-lactams, cephamycins | KPC-2, IMI-1, SME-1 |

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| Bush-Jacoby group (2009) | Bush-Jacoby-Medeiros group (1995) | Molecular class (subclass) | Distinctive substrate(s) | Inhibited by | | Defining characteristic(s) | Representative enzyme(s) |
|---|---|---|---|---|---|---|---|
| | | | | CA or TZB[a] | EDTA | | |
| 3a | 3 | B (B1) | Carbapenems | No | Yes | Broad-spectrum hydrolysis including carbapenems but not monobactams | IMP-1, VIM-1, CerA, IND-1 |
| | | B (B3) | | | | | L1, CAU-1, GOB-1, FEZ-1 |
| 3b | 3 | B (B2) | Carbapenems | No | Yes | Preferential hydrolysis of carbapenems | CphA, Sfh-1 |
| NI | 4 | Unknown | | | | | |

[a] CA, clavulanic acid; TZB, tazobactam
[b] NI, not included.

enzyme due to its increasing prevalence in the last 20 years. It belongs to Ambler class A and D. The third group is also known as metallo-β-lactamase (MBL), which has unique structures, and functions, that requires zinc in their active site, and have the ability to hydrolyze carbapenem. However, nowadays several serine-β-lactamase also have this ability. The difference between them is that MBL has low monobactam hydrolyzing ability and cannot be inhibited by clavulanate acid and tazobactam. According to Ambler classification, they belong to class B. The fourth group of ESBL is present in the previous classification of 1995 but has been omitted in the latest scheme. This enzyme might be categorized into different classification if sufficient data is available.[8,9]

## TYPES OF ESBL

The type of ESBL that is commonly found is Temoneira (TEM). About 90% of *E. coli*, which are resistant to ampicillin, occurred due to the production of TEM-1. This type has the ability to hydrolyze penicillin and first generation of cephalosporin but not cephalosporin oxymino. Although it is usually found in *E. coli* and *K. pneumonia*, frequency of TEM type β-lactamase is also increasing in other gram-negative bacteria. Until recently, there are 140 TEM type is known. The second type is Sulfhydryl variable (SHV) whose 68% of its amino acid is similar to TEM type. Most commonly found in *K. pneumonia* is SHV-1 that cause resistance towards penicillin, tigecycline and piperacillin but not cephalosporin oxymino. There are 60 SHV type known so far in Europe, America and in the whole world. The TEM-1 and SHV-1 type have the ability to inactivate ampicillin, and some of them may experience further mutation that will lead to expansion of β-lactamase activity. This explains why there are other types of TEM and SHV that also cause the third generation of cephalosporin and aztreonam inactivation.[10-13]

The Cefotaxime hydrolyzing capabilities (CTX) type has stronger ability in hydrolyzing cefotaxime, and may be inhibited by tazobactam as β-lactamase inhibitor. There are more than 80 CTX type known so far. The CTX-M enzyme is not limited to nosocomial infection only but have the potency to spread in the community (usually by *E. coli*) and this has become a public health problem. According to a survey in 2000, the prevalence of ESBL-E in community of European countries has increased. A study by Ben-Ami et al[14] in Israel found that 14% of ESBL infection have community onset. This study also showed that there was an increased risk of infection in nursing homes. Furthermore, Rodriguez-Bano et al[15] did an analysis between the uses of BL antibiotics and β-lactam inhibitors (BLI) as a combination compared to carbapenem in treating infections caused by ESBL-EC in the year of 2011 towards 103 Spanish patients, and found that 51% cases occurred in the community

due to CTX-M. Moreover, Severin et al[16] did a research about the characteristics of ESBL-EC and ESBL-KP infections in Surabaya and found that the prevalence of CTX-M-15 in ESBL-EC is 94.5% and ESBL-KP is 55.6%.[11-12]

Oxacillin hydrolyzing capabilities (OXA) β-lactamase is a less commonly found type, and has different characteristics from TEM as well as SHV since it belongs to Ambler class D. This type has the ability to hydrolyze oxacilin and cloxacillin, and cannot be inhibited by clavulanate acid. It is mainly found in *P. aeruginosa*, mostly in Turkey and France, but also present in other gram-negative bacteria such as 1-10% *E. coli* producing OXA-1. Several other ESBL that is transmitted through plasmid, such as *Pseudomonas* extended resistant (PER), Vietnam ESBL (VEB), Guiana extended-spectrum (GES) and integron-borne cephalosporinase (IBC) are rarely found and have very limited transmission.[10-12]

## ESBL MECHANISMS OF RESISTANCE

Bacteria may become resistance to β-lactam antibiotics through several mechanisms. Most commonly found is through the destruction by β-lactamase enzyme in the periplasm of gram-negative bacteria. This enzyme has higher affinity towards antibiotics than antibiotics to their target. The binding of this enzyme will cause β-lactam ring to hydrolyze. The gene coding β-lactamase is found in the chromosomes and extra-chromosomes, and usually a mobile element. This ESBL resistance may be acquired in a mobile genetic element (such as in *K. pneumoniae and E. coli*) or in an immobile genetic chromosomes (in Enterobacter species), and have the ability to hydrolyze penicillin and cephalosporin. One of the strategy to counteract this mechanism is by using inhibitors that bind to these enzyme, however inhibitors such as clavulanate acid, sulbactam and tazobactam do not bind to all β-lactamase in the chromosomes, hence cannot fully prevent inactivation of BL antibiotics by this enzyme. There is no BL/BI combination known so far has the ability to inhibit all β-lactamase enzyme.[17,18]

Other mechanisms include coupling in gram-negative bacteria where there is reduced membrane permeability with fast antibiotics reflux from periplasm to exterior of the cell. This mutation will cause decreased amount of BL antibiotics that goes into the cell, along with increased amount of channels pumping out the antibiotics outward. This mechanism also happens in the resistance of ESBL-E towards quinolone and aminoglycoside.[18]

## DETECTION OF ESBL

Identification of ESBL-E is a problem in hospitals and laboratory facilities despite its importance in therapeutic approach and infection control to prevent their spread. Most guidelines recommend specimen screening based on reduced sensitivity towards cephalosporin and followed by one of the tests available to confirm the presence of ESBL-E. However, it is still not known which method should be used.[19]

According to National Committee for Clinical Laboratory Standards (NCCLS); which is changed into Clinical and Laboratory Standards Institute (CLSI) in 2005, mentioned that ESBL screening should be routinely done. Recommendation by CLSI shows that ESBL detection is consists of two steps, the first is screening for reduced sensitivity to certain antibiotics used such as cefotaxime, ceftriaxone, ceftazidime, or aztreonam. The next step is to do a confirmatory test only if positive screening result is found. The aim of confirmatory test is to detect hydrolyzing potential by ESBL towards antibiotics that are used in screening in the presence of BLI. Several type of tests are recommended by CLSI, however until now there is no gold standard examination to detect ESBL.[20-22]

Screening test of ESBL may be done using Vitek, and positive result is when there is a resistance towards cephalosporin and aztreonam. Positive or negative result is evaluated using Advanced Expert System. Moreover, Kirby-Bauer disks, according to CLSI recommendation, can also do screening test.[23,24]

Confirmatory test may be done using double-disk synergy test (DDST), combination disk method, or E-test ESBL strip. The DDST test is performed on agar with a 30 μg disk of cefotaxime (and⁄or ceftriaxone and⁄or ceftazidime and⁄or

aztreonam) and a disk of 10μg of clavulanate acid positioned at a distance of 30 mm (centre to centre). The test is considered as positive when a decreased susceptibility to cephalosporin is combined with a clear-cut enhancement of the inhibition zone in front of the clavulanate acid-containing disk (**Figure 1**). Whereas the evaluation of combination disk method is by measuring the inhibition area around disk containing cephalosporin and disk containing cephalosporin and clavulanate acid. Usually both disks are located at a distance of ≥5 mm (centre to centre), and positive result is when the area enlarged until 50% (**Figure 2**). Confirmatory test may also be done using E-test ESBL strip. Two-sided strips are used in this method, containing cefotaxime, cefazidime or cefepim, either alone at one end of the strip, or combine with clavulanate acid on the other end. The E-test ESBL strip is considered as positive when there is a phatom zone in the lowest concentration of antibiotic with clavulanate acid or when the minimum inhibitory concentrations (MIC) is reduced by more than two-fold in the presence of clavulanate acid (**Figure 3**).[23]

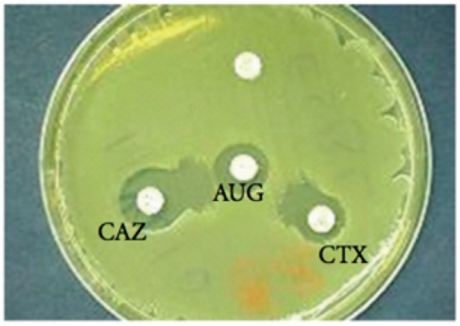


**Figure 1.** Double-disk synergy test (DDST) method[7]

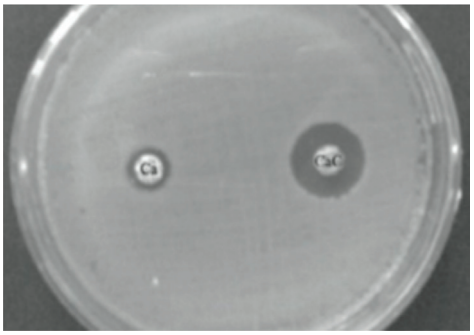

**Figure 2.** Combination disk method[24]

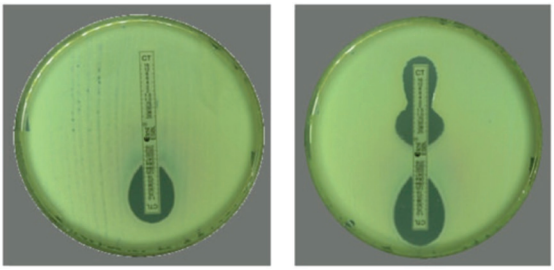

**Figure 3.** E-test ESBL strip[7]

A study by Garrec et al[19] in a hospital in France, compared different phenotype method in the detection of ESBL-E. It was mentioned that Vitek is considered as a routine method in the detection of ESBL with sensitivity 92-93% and low specificity that is 50-79%. However, E-test has the sensitivity of 71-73% in testing cefotaxime and ceftazidim, and 90% for cefepime. Another method is combination disk methods with sensitivity 100% in testing cefotaxime and cefepim towards ESBL-E. Double-disk synergy method has better sensitivity but the distance of how the disks should be positioned still need recommendation by microbiologists.

Phenotype confirmatory tests, as mentioned before, cannot identify specific enzymes causing the production of ESBL. Therefore, genotype confirmatory tests is also important, and may be done using polymerase chain reaction (PCR) followed by sequencing to differ variants of those specific enzymes. Several other methods include PCR with restriction fragment length polymorphism analysis (PCR-RFLP) and PCR with single-strand conformational polymorphism analysis (PCR-SSCP). Nevertheless, subtypes of ESBL continue to grow hence these methods have develop limitation; which made detection of ESBL become complex and difficult due to variety of mutation process.

## RISK FACTORS OF ESBL COLONIZATION AND INFECTION

Infections due to ESBL-E are usually nosocomial and most commonly found in intensive care units (ICUs), and related to the length of stay, increased cost and mortality. Several risk factors mentioned by Park et al[26] in their study on all bacteremia patients in Korean hospitals since January 2005 until

March 2009 include geriatrics, diseases such as liver cirrhosis and malignancy that usually need long hospital care, airway and urinary tract infections, use of catheter and naso-gastric tube (NGT), severe sepsis and use of third generation of cephalosporin and quinolone in the last 3 months during hospital stay. Similar things also communicated by Muro et al[27] in their research among 90 patients in Mexico with ESBL infections known from their blood culture results, and found that several risk factors causing this infection are the use of catheter and intravenous line, hospital length of stay more than 15 days, underwent surgery, and use of cephalosporin.

Whereas in a study by Freeman et al[28] of 206 patients with culture result of ESBL-EC and ESBL-KP in 3 different hospitals in New Zealand from 2009 until 2011, obtained that patients experienced ESBL-EC usually occur due to community infection or with chronic pulmonary infection in high prevalence country. On the other hand, infection due to ESBL-KP is usually related to ICU admission, surgery and transmission within health care facilities.

Recently, several cases of ESBL-E in the community have been reported. Comparison of the characteristics and risk factors due to ESBL-E in the community and nosocomial are summarized in **Table 2**.[25]

## MANAGEMENT OF ESBL INFECTIONS

Until recently, choices of antibiotics available to treat ESBL-E infections are still limited. According to European antimicrobial resistance survey in 2011 from culture results that the prevalence of third generation of cephalosporin in *E. coli* and *K. pneumoniae* are 9.1% and 30.1%; in ESBL-EC is 85-100% and ESBL-KP is 62.5-100%. Resistance of *E. coli* towards carbapenem, quinolone and aminoglycosides are 0.04%, 20.9% and 9.3% respectively; whereas resistance of *K. pneumoniae* towards carbapenem, quinolone and aminoglycosides are 9.1%, 30.5%, and 26.2%, respectively. Because resistance towards first line of antibiotics treatment is increasing, therefore choice of empirical antibiotic treatment has become more difficult. Empirical antibiotic treatments should be based on antibiogram in different institution and usually varies from one hospital to another in different city and countries.[25,29]

Several studies mentioned that cephalosporin still can be used because ESBL type TEM and SHV have low MIC towards cefotaxim. However, CLSI recommends that all ESBL-E should be considered as resistant to cephalosporin without considering their MIC because the use of cephalosporin is related to high treatment failure and mortality. This is occurred due to inoculum effect in bacteria with the ability to destroy the antibiotics. When bacteria die and destroy the antibiotics at the same time, cellular enzyme will be released and may reduce antibiotics concentration. In vitro test to evaluate bacteria's ability to counteract antibacterial activity by BL antibiotics is determined by 2 factors, which are antibiotics intrinsic activity toward bacteria tested and antibiotic susceptibility to hydrolyze β-lactamase enzyme. In general, the higher the inoculum effect, the easier certain antibiotics to be hydrolyzed by ESBL.[30,31]

**Table 2.** Characteristics of ESBL-E infections[25]

| Onset | Community acquired | Hospital acquired |
|---|---|---|
| Organism | *Escherichia coli* | Klebsiella spp |
| Type of ESBL | CTX-M (mostly CTX-M15) | Mostly SHV and TEM |
| Infection | Majority is urinary tract infection | Airway and intra abdominal infection |
| Susceptibility | Resistance to all penicillin and cephalosporin, also several other antibiotics including fluoroquinolone | Resistance to all penicillin and cephalosporin, also several other antibiotics including fluoroquinolone |
| Risk factors | Recurrent urinary tract infection, use of broad-spectrum antibiotics such as cephalosporin, fluoroquinolone, hospital length of stay, live in nursing homes, geriatrics, and diabetes mellitus. | Long hospital length of stay especially in intensive care units, use of ventilator, catheter and use of broad-spectrum antibiotics such as cephalosporin. |

Carbapenem is the choice of treatment in critically ill patients due to ESBL-E infections, and usually have lower treatment failure with better results. Vardakas et al[32] analyzed several studies on comparison between carbapenem and alternative antibiotics in treating ESBL-E infection, and found that empirical and definitive therapy with carbapenem have lower mortality compared to the use of combination non β-lactam antibiotics (non-BL) and BLI. Carbapenem, such as imipenem, meropenem and doripenem are now commonly used as empirical therapy for nosocomial infection due to ESBL-E.[30,32-33]

Infections caused by ESBL is considered as serious problem in treating infectious patients in a matter of choosing the appropriate antibiotics, which leads to increased use of carbapenem that creates new problem that is *Enterobacteriaceae* resistance to carbapenem, which of course will cause further difficulties in choosing antibiotics. In order to prevent this carbapenem resistance, the use of BL/BLI combination has come into consideration. Combination of BL/BLI, such as amoxicillin-clavulanate (AMC) or piperacillin-tazobactam (PTZ) may be used to handle infection due to ESBL-E. Tamma et al[34] underwent a research in the year of 2007 until 2014 in 213 American patients that were divided into 2 groups, where the first group was given PTZ as empirical therapy then switched to carbapenem in 84 hours and the second group was treated with carbapenem from the beginning. A fourteen days mortality analysis was made, with results of higher mortality rate in the group initially treated with PTZ. This is different from a study by Rodriguez-Bano et al[15] that analyze comparison of treatment between BL/BLI and carbapenem to treat ESBL-EC in 2011 in Spain among 103 patients and displayed that BL/BLI may be used as alternative treatment. Comparable results was showed by Vardakas et al[32] dan Shiber et al[35] that there is no difference in mortality rate between carbapenem and BL/BLI. Until lately, there are still limited publications on the use of BL/BLI in treating ESBL-E hence carbapenem is still considered as treatment of choice.[30]

Analyses conducted on ESBL infection produce variety of results. In a study by Kumar et al[36] on 180 patients with ESBL infection in India, obtained that 100% cases are susceptible to imipenem. This study also showed ESBL susceptibility pattern to other anitbiotics such as PTZ is 87.2%, cefoperazone/sulbactam 76.7%, AMC 75.55%, ceftazidime/clavulanate 66.11%, and aminoglycoside that is amikacin 73.17% and gentamycin 60%.

Fosfomycin is also known to have bactericidal effect against *Enterobacteriaceae*. Falagas et al[37] underwent a study on 4448 patients with ESBL-E infections and acquired that 90% cases are susceptible to fosfomycin. Based on CLSI criteria, it was mentioned that ESBL-E are susceptible 91.3% from 11 studies available. Fosfomycin given with dosage of 2-4g every 6 hours also can be used to treat *K. pneumonia* carbapenemase (KPC) shown in a study by Michalopoulos et al.[38] This also shown by Neuner et al[39] in their study in 41 patients with urinary tract infection cased by ESBL-E or KPC, and found that 92% are successfully treated with fosfomycin.

Nitrofurantoin is considered as another choice of antibiotics to treat urinary tract infections caused by ESBL-E. In a study by Tasbakan et al[40] showed that nitrofurantoin has good clinical response in patients with uncomplicated urinary tract infection due to ESBL-EC. In a study by Kulkarni et al[24] toward 265 patients with ESBL (known from culture results), found that resistance test to nitrofurantoin is 75% and amikacin is 70.4% whereas gentamycin is only 19.4%. However, there are not enough studies on the use of nitrofurantion and aminoglycoside in the management of ESBL-E infection hence they are still rarely used.

A study by Reinert et al[41] as part of TEST study towards patients in health care centers of Asia Pacific, North America, America Latin and Europe, found that about 94.3-97.1% ESBL-E is susceptible to tigecycline. Whereas a study by Corvec et al[42] mentioned that fosfomycin, tigecycline, and colistine can be use to treat ESBL, however tigecycline cannot be used as single antibiotic therapy to treat infections caused by gram-negative bacteria. If combined with colistine, tigecycline may give out better result in infection due to ESBL-KP

and MBL. This, of course, will make tigecycline a choice of treatment in managing ESBL-E infection. However, tigecycline is commonly used in treating MRSA and also infection due to carbapenem-resistant bacteria hence it is not recommended as a first line antibiotic.[43]

In Indonesia, Kuntaman et al[44] did a study on susceptibility pattern of ESBL towards commonly used antibiotics in 300 ESBL infected patients in Surabaya and Malang in 2010. Sensitivity of ESBL-EC and ESBL-KP towards meropenem was 100% and 96.5% respectively, towards cefoperazone-sulbactam, were 97.7% and 94.4%, towards fosfomycin were 95.3% and 94.4%, towards amikacin were 90.6% and 86.6%, towards ciprofloxacin were 26.6% and 53.3%, whereas towards cefotaxime were 3.22% and 4.23% respectively. From those data, it can be concluded that meropenem is the main choice of therapy in managing infection due to ESBL-E, however fosfomycin, combination of BL/BLI and amikacin can also be used. Treating those patients with cephalosporin and fluoroquinolon should be prohibited, based on CLSI recommendation even if they seem to be sensitive in the culture results.

## PREVENTION

Increasing of ESBL-E may happen easily within hospital environment, especially through medical staffs contaminated hands that will extent infection between patients. Distribution can also occur through health equipment, such as thermometer, endoscopy instruments and bath utensils. Consequently, when and how to perform steps of washing hands properly and how to sterilized medical apparatus should be applied in daily clinical practices. Hospitals have the responsibility suppress the incidence of ESBL-E infection one of which by isolating infected patients to prevent further spread.[45]

High prevalence of antibiotic resistance and inadequate choice of available antibiotics necessitate clinicians to use antibiotic wisely. Antimicrobial stewardship program (ASP) improve antibiotic use by shortens the duration of antibiotic therapy, limits the use of broad-spectrum antibiotics and monitors appropriate use of antibiotic. Nowadays, Centers for Disease Control and Prevention (CDC) have recommended ASP availability in every hospital.[46]

## CONCLUSION

Infection due to bacteria that resistant to multiple antibiotics is a rising worldwide problem, particularly nosocomial infection caused by ESBL-E. The prevalence of ESBL-E continues to increase, mainly in Asian countries. Detection of ESBL-E infection requires complex evaluation, consists of screening and confirmation. However, subtypes of ESBL-E keep growing thus methods available have become restricted; which cause detection to be even more challenging due to variety of mutations. This will of course make choosing antibiotic becomes problematic. Most studies show great results with carbapenem therapy, nevertheless, other antibiotics, for example BL/BLI combination, like PTZ, and fosfomycin also show good results, so they can also be used to treat ESBL-E infection. Carbapenem should only be used in serious and life threatening infections in order to reduce carbapenem resistant, even if it still rarely found, particularly in Asia.

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