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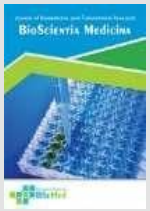

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Diagnosis and Treatment-Spectrum Beta-Lactamase and Multidrug Resistance Bacterial

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A B S T R A C T

Multidrug-resistant (MDR) is a condition resistant to at least one type of antibiotic from 3 classes of antibiotics. Extended-Spectrum Beta Lactamases are globular proteins that consist of alpha-helices and beta-pleated sheets. β-lactamase hydrolyze broad-spectrum cephalosporin with oxyimino side chain. ESBL hydrolyze antibiotics group penicillin, cephalosporin first, second, third, fourth generation, and monobactam aztreonam. Multidrug resistance occurs through two mechanisms, bacteria accumulate multiple genes encoding resistance to one antibiotic, and due to increased expression of genes encoding multidrug effluent pump, enzymatic inactivation and target structure change. Multidrug-resistant (MDR) caused by extended-spectrum resistance beta-lactamase (ESBL) can be detected by phenotyping and genotyping methods. Treatment for MDR ESBLs other than carbapenems can be β-lactam/β-lactamase inhibitor combinations (BLBLIs), namely piperacillin/tazobactam (PZT).

1. Introduction

Antibiotics are drugs used for prophylaxis and therapy in bacterial infections. Salvarsan was the first antibiotic discovered by Ehrlich in 1910. Then in 1928, Alexander Fleming developed the discovery of penicillin which inhibits the growth of Staphylococcus aureus. In 1935 Gerhard Domagk developed sulfonamides, then discovered the aminoglycoside streptomycin, chloramphenicol, tetracycline, macrolides, and glycopeptides such as vancomycin in the 1940s. The first anti-tuberculosis drug, streptomycin, was discovered by Wakzman and Schatz in 1943.[1,2]

The development of antibiotics was followed by an increase in antibiotic resistance, and penicillin resistance was first discovered in 1950. However, due to the innovation of scientists, in 1962, many new antibiotic agents were developed, such as quinolones, nalidixic acid, and broad-spectrum β-lactam antibiotics. such as cephalosporins, monobactams, and carbapenems.[1,2]

Antibiotics are classified into six groups, namely sulfonamides, quinolones, beta-lactams, tetracyclines, macrolides, and aminoglycosides. Based on the mechanism of action, antibiotics are divided into five groups, namely (1). Antibiotics that interfere with microbial cell metabolism, (2). Antibiotics that inhibit the synthesis of microbial cell walls, (3). Antibiotics that interfere with the permeability of microbial cell membranes; (4) Antibiotics that inhibit microbial cell protein synthesis, and (5). Antibiotics inhibit the synthesis or damage the microbial acid core cells.[3,5]

Multidrug-resistant

Multidrug-resistant (MDR) is a condition that is resistant to at least one type of antibiotic from 3 classes of antibiotics. Multidrug resistance is classified into primary and secondary resistance (1). Primary resistance occurs in organisms that do not use the appropriate antibiotic for their host. (2). Secondary resistance, or "acquired resistance," resistance that occurs due to previous use of antibiotics. Further classified as a). Intrinsic resistance, resistance to first-line antibiotics used to treat disease based on clinical evidence, eg, Mycobacterium tuberculosis is resistant to rifampin and isoniazid. b). Broad resistance is minimal resistance to one or two of the most effective antibiotics or also known as drug resistance (XDR). 3). Clinical resistance occurs due to inappropriate use of antibiotics or failure of antibiotic therapy due to a decrease in the effective immune system. In other words, the pathogen can only be inhibited by antibiotics with concentrations higher than normal doses.[5]

Pathogenesis multidrug-resistant

Antibiotics inhibit metabolisms such as nucleotide synthesis, which inhibits DNA/RNA and protein synthesis and damages cell membranes or competes with substrate enzymes involved in cell wall synthesis (eg, chitin synthase). Based on the mechanism of resistance, antibiotic resistance is divided into four types, 1). Intrinsic resistance is caused by the structural characteristics of bacteria that are incompatible with antibiotics. Mechanisms are determined by genes on bacterial chromosomes such as Amp C β-lactamase from gram-negative bacteria and efflux systems that are resistant to many drugs such as vancomycin which cannot cross the membrane so that gram-negative bacteria are intrinsically resistant to vancomycin 2). Acquired resistance occurs due to changes in bacterial genetic mutations or resistance that occurs because they do not respond to previously responsive antibiotics. Co-acquired resistance Becomes chromosomal resistance and extrachromosomal resistance (plasmids, transposons, etc.). 3). Cross-resistance occurs when antibiotics have the same mechanism of action as other antibiotics. Such as between resistance to erythromycin, neomycin, and kanamycin or resistance between cephalosporins and penicillins. 4). Multidrug resistance and pan resistance that occurs in several groups of antibiotics are usually used to treat them.[6.7,8]

Multidrug resistance to bacteria could occur through two mechanisms. First, bacteria accumulate multiple genes encoding resistance to one drug. This type of resistance usually occurs in plasmid resistance. Second, it occurs due to increased expression of genes encoding multidrug effluent pump, enzymatic inactivation, target structure change, etc. The mechanism of antibiotic resistance is described in the following table.[8]

Table 1. Mechanism resistance antibiotics[7]

Mechanism	Antibiotics resistant
Limitation concentration drug intracellular increase efflux	tetracyclines, (eg , tetA genes) Quinolones (eg , norA genes)
Decrease permeability membrane outside on basil grams negative with change channel porin	β-lactams (eg , omF, oprD genes) Quinolones (eg , omF genes)
Decrease transport membrane cytoplasm	Aminoglycosides (decrease energy)
Inactivity (reversible) or (irreversible)	β-lactams (ß-lactamases), Aminoglycosides (change enzyme)Chloramphenicol (inactive enzyme)
Change antibiotic targets	Quinolones (gyrase change), Rifampin (DNA polymerase binding), β-lactams (PBP gene changes), Macrolides (rRNA methylation)
Bypass of antibiotics target	Glycopeptides (vanA, vanB genes) trimethoprim (thymidine-deficient strains)

Extended-spectrum beta-lactamase

Extended-spectrum beta-lactamase (ESBL) is a globular protein consisting of an alpha-helix and a beta-pleated sheet. β-lactamases hydrolyze broad-spectrum cephalosporins with oxyimino side chains. ESBL hydrolyzes the penicillin class of antibiotics, first, second, third, and fourth-generation cephalosporins and monobactam aztreonam. ESBLs originate from mutations in TEM-1, TEM-2, or SHV-1 that result in changes in the amino acid configuration of the β-lactamase enzyme. ESBLs are classified in group 2be on the Bush-Medeiros-Jacoby system and class A on the Ambler system. The point mutations of SHV and TEM β-lactamase lead to single amino acid substitutions (Asp104 → Lys, Arg164 → Ser, Arg164 → Nya, Asp179 → Asn, Gly238 → Ser, and Glu240 → Lys), leading to resistance. The broad spectrum classification of beta-lactamase is described in the following table.[9]

Table 2. Classification of extended-spectrum beta-lactamase[9]

Bush-Jacoby-Medeiros System	Major subgroups	Ambler system	Main attributes
Group 1 cephalosporinases	-	C (cephalosporinases)	Usually chromosomal; Resistance to all β-lactams except carbapenems; not inhibited
Group 2 penicillins (clavulanic acid susceptible)	2a	A (serine β-lactamases)	Staphylococcal penicillinase
	2b	A	Broad-spectrum-TEM-1, TEM-2, SHV-1
	2be	A	Extended-spectrum-TEM-3-160, SHV-2-101
	2br	A	inhibitor-resistant TEM(IRT)
	2c	A	Carbenicillin-hydrolyzing
	2e	A	Cephalosporinase is inhibited by clavulanate.
	2f	A	Carbapenemases inhibited by clavulanate
	2d	D (oxacillin-hydrolyzing)	Cloxacillin-hydrolyzing (OXA)
Group 3 Metallo-b-3a B (metalloenzymes)	3a 3b 3c	B (metalloenzymes) B B	Zinc-dependent carbapenemases
Group 4		Nor classified	Miscellaneous enzymes, most not yet sequenced

In the year 2014, The clinical & laboratory standards institute and the European Committee on antimicrobial susceptibility testing develop the ESBL screening method using the disc diffusion and microdilution screening tests using agent antibiotics like cefpodoxime, ceftazidime, aztreonam, cefotaxime, and ceftriaxone which will then be confirmed use clavulanate acid and cephalosporins. Detection of Extended-spectrum beta-lactamase (ESBL) through screening and confirmation is described in the following charts and tables.[10-12]

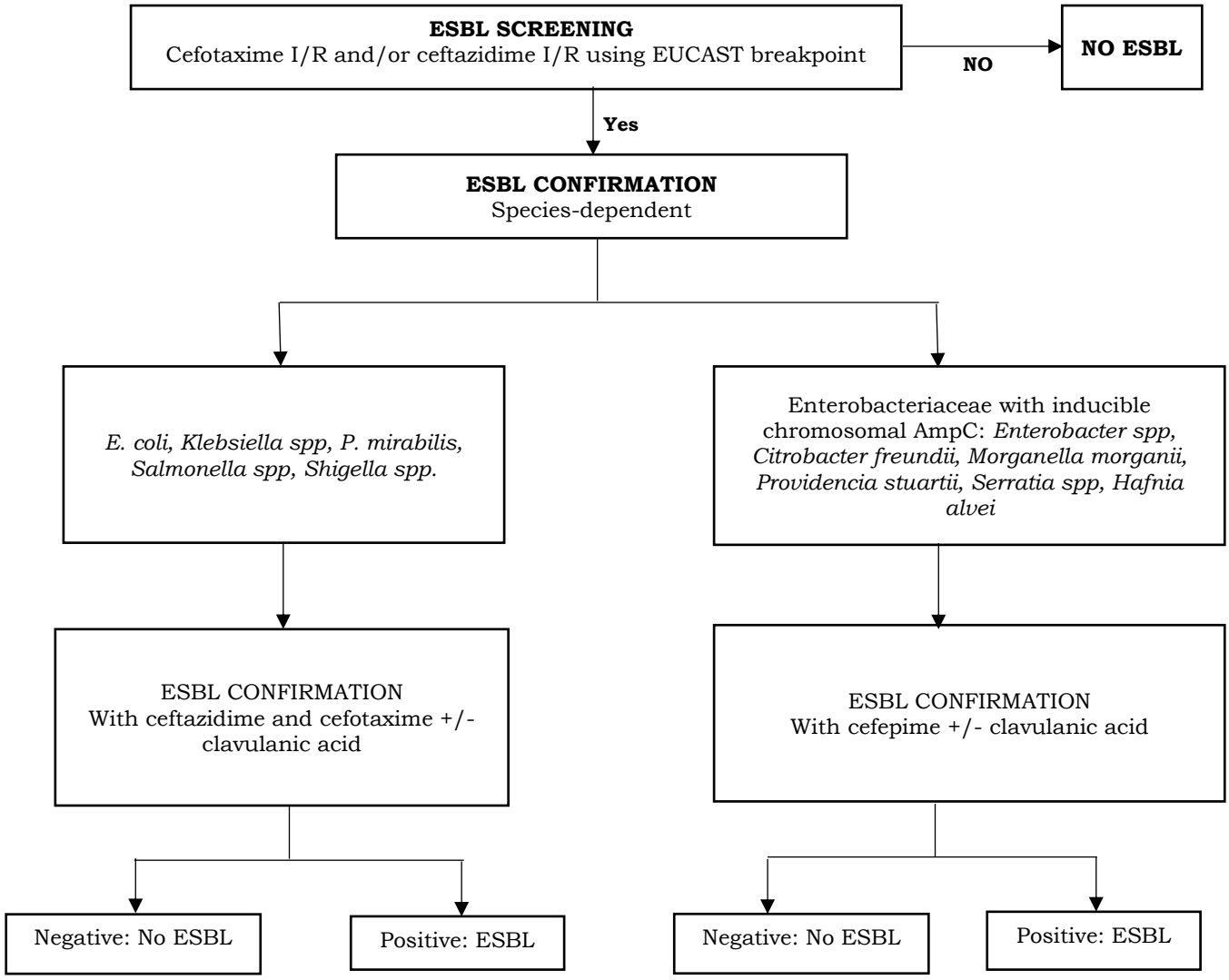

Figure 1. Detection of extended-spectrum beta-lactamase[11]

The extended-spectrum beta-lactamase screening method is divided into two groups. (a). group I Enterobacteriaceae (*E. coli, Klebsiella spp., P. mirabilis, Salmonella spp., Shigella spp.*). (b). group II (*Enterobacter spp, Citrobacter freundii, Morganella morganii, Providencia spp, Hafnia alvei*). The method recommended are broth dilution media, agar, and disk diffusions such as Microscan (Siemens), Phoenix (Becton-Dickinson), or VITEK 2 (bioMérieux) with antibiotics, and the zones of inhibition are described in the following table.[11]

Table 3. Screening disc extended-spectrum beta-lactamase [13]

EUCAST recommended			**CLSI recommended**			
Antibiotic disc		conduct ESBL-testing if	Antibiotic Disc		Conduct ESBL-testing if	
Cefotaxime	CTX 5 g	inhibition zone < 21 mm	cefotaxime	CTX 30 g	*/**	inhibition zone 27 mm
			ceftriaxone	CRO 30 g	*	inhibition zone 25 mm
Ceftriaxone	CRO 30 g	inhibition zone < 21 mm	ceftazidime	ACZ 30 g	*/**	inhibition zone 22 mm
			aztreonam	ATM 30 g	*	inhibition zone 27 mm
Ceftazidime	CAZ 10 g	inhibition zone <22 mm	cefpodoxime	PX 10 g	**	inhibition zone 22 mm
Cefpodoxime	PX 10 g	inhibition zone <21 mm	**Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli* ***Protesu mirabilis*			

The confirmation method is done if there is an inhibition zone on screening. The confirmation method is done in two ways (1). phenotype confirmation is a method based on in vitro activity of ESBL inhibitor used clavulanic acid and the combination disk test (CDT) method, the double-disk synergy test (DDST), the Etest ESBL and broth microdilution test. (2). Genotypic confirmation is the method carried out with gene sequencing PCR or DNA microarray-based methods. On microarray Check- KPC ESBL (Check-Points, Wageningen, The Netherlands), test results were obtained within 24 hours. ESBL confirmation methods for positive ESBL screening tests are described in the following table.[10,13-15]

Table 4. Method ESBL confirmation for test screening ESBL positive.[13]

Method	**Antimicrobial agent (disk content)**	**Confirmation is positive if**
Etest ESBL	Cefotaxime +/- clavulanic acid	MIC ratio ≥8 or deformed ellipse present
	Ceftazidime +/- clavulanic acid	MIC ratio ≥ 8 or deformed ellipse present
Combination disk diffusion test (CDT)	Cefotaxime (30 g) +/- clavulanic acid (10 g)	≥5 mm increase in inhibition zone[2]
	Ceftazidime (30 g) +/- clavulanic acid (10 g)	≥5 mm increase in inhibition zone[2]
Both microdilution	Cefotaxime +/- Clavulanic acid (4 mg/L)	MIC ratio ≥ 8
	Ceftazidime +/- Clavulanic acid (4 mg/L)	MIC ratio ≥8
	Cefepime +/- Clavulanic acid (4 mg/L)	MIC ratio ≥ 8
Double disk synergy test (DDST)	Cefotaxime, ceftazidime and cefepime	Expansion of indicator cephalosporin inhibition zone towards amoxicillin-clavulanic acid dist.

Management multidrug-resistant extended-spectrum beta-lactamase

Antibiotic therapy

Current antibiotic therapy in ESBL infection is carbapenems and β-lactam/β-lactamase inhibitor combinations (BLBLIs), especially piperacillin/tazobactam (PZT) cefepime, cephamycins, and fosfomycin. Piperacillin/tazobactam and cefepime are non-carbapenem which are the most frequently used.[16-18]

Carbapenem

Carbapenems are currently the standard therapy for severe infections caused by ESBL-producing bacteria. Carbapenems are resistant to hydrolysis ESBL and were not affected by the inoculum effect. Studies show carbapenem is the gold standard for severe Enterobacteriaceae infection and invasive ESBL. The side effects of carbapenems are epileptogenic effects.[16.19]

Imipenem or meropenem is the main choice in patients with a history of seizures, pregnancy, or other disorders of kidney function due to fewer side effects on the central nervous system, less toxicity in pregnancy, and their adjustment dose on imipenem. Doripenem is a carbapenem which relatively new. Clinical data using doripenem on ESBL infection show the efficacy equivalent to meropenem or imipenem. Pana ZD et al. (2018), cohort retrospective study shows Ertapenem is as effective as other carbapenems in empirical and targeted therapy bacteremia in Enterobacteriaceae infection producer ESBL. Gutierrez Research- Gutierrez et al. (2016), showing the efficacy of ertapenem 90.6% is similar to that of other carbapenems 75.5%. Efficacy level carbapenem on therapy empirical 89.8% and on bacteremia target 82.6%.[16,20]

Combination β-lactam / β-lactamase inhibitor (BLBLI)

Carbapenems are used in the treatment of severe infections caused by bacteria-producing ESBL. It becomes a big problem if carbapenems are resistant. The latest study shows that BLBLI, like amoxicillin/clavulanate (AMC) or piperacillin/tazobactam effective against bacteria producer ESBL and becomes an alternative another carbapenem for the treatment bacteremia ESBL.[20]

Piperacillin/tazobactam

Piperacillin-tazobactam (PTZ) is an alternative carbapenem-sparing against ESBL infection. PTZ has in vitro activity with appropriate breakpoints according to clinical & laboratory standards institute (CLSI) to Enterobacteriaceae producing ESBL is 16/4 mg/l (susceptible), 32/4 - 64/4 mg/l (intermediate), and 128/4 mg/l (resistant). Multicenter clinical trial (MERINO) in Europe microbiology clinic & disease infectious congress in the 2018 year show the most Enterobacteriaceae producing ESBL bacteremia source is the urinary tract (60.9%) with a predominance of *E. coli* 86.5% and a mortality rate of 30 days between treatment with PTZ was higher 12.3% compared meropenem 3.7%.[16,20]

Amoxicillin/clavulanate

Amoxicillin/clavulanate or Co-Amoxiclav is the first choice of antibiotics for treating ESBL infections. Amoxicillin has no inoculum effect that causes the level of bacteremia of *E. coli* producer ESBL and non-ESBL permanent high. In vitro, in-time-kill research shows PTZ has an effect better inoculum against *E. coli* than amoxicillin.[21]

Cefoperazone/sulbactam

Cefoperazone/sulbactam is a combination β-lactamase inhibitor widely used in Asia. observational study in India demonstrated the efficacy of cefoperazone/sulbactam similar to carbapenems in threatening ESBL infection (85,71 and 79.64% P = 0.152). Research by Lai CC et al. (2018), multidrug resistance bacteria isolates such as *Escherichia coli* producer ESBL, *Klebsiella pneumoniae* producer ESBL, Enterobacteriaceae resistant carbapenems,

Pseudomonas aeruginosa resistant carbapenem and Acinetobacter baumannii resistant carbapenems, showing the addition of sulbactam increased the activity of cefoperazone against bacteria multidrug-resistant.[20.22]

Beta-lactams

Cefepime

Cefepime is the only cephalosporin expanded spectrum which great stability against ESBL. The dosage standard recommended according to CLSI to cefepime treated ESBL is MIC 2 mg/l. The dose often used is 4 and 8 mg/l. Research by Lee, et al, and Wang, et al, showed a mortality rate in cefepime 16.7% with MIC < 1 g / mL, 45.5% with MIC 2-8 g/mL and 100% with MIC 16 g/mL, (p = 0.035). research by Yu Bin Seo et al. (2017) shows that cefepime efficacy is 33.3% inferior to PTZ and ertapenem at 94%.[23-24]

Cephamycins

Cephamycins such as cefmetazole and flomoxef have stable activity hydrolytic ESBL. Sheu CC et al. (2018), a retrospective study in Taiwan, compared flomoxef with carbapenems in patients with *E. coli* bacteremia, and ESBL-producing K. pneumoniae showed that flomoxef was inferior compared with carbapenems with flomoxef breakpoint MIC 8 mg/l.[20]

Fosfomycin

Fosfomycin is a bactericide antibiotic (phosphonates acid) that inhibits wall cell biosynthesis with low molecular weight, low hydrophilic, and no bond with protein serum. Fosfomycin has a stable penetration ability to the cell. Fosfomycin inhibits bacteria gram-negative such as *E. coli* producing ESBL 81 - 100% with MIC 90 doses 2 - 4 mg/L. in Asia, the MIC of the resistance inhibitor is greater than 128 mg/L and K. pneumoniae producer ESBL 15 -100% with MIC 90 of 32 - > 1,024 mg/L. Research show inhibiting power of fosfomycin compared to carbapenem has no significantly different effect on the treatment of Enterobacteriaceae producing ESBL based on break point susceptible clinical and microbiology.[20, 22]

Novel β-lactam / β-lactamase (BLBLI)

The United States Food and Drug Administration recommended 2 BLBLIs, ceftolozane/tazobactam and ceftazidime/avibactam, in 2015 for treatment complications of Intra abdomen infection and urinary tract infections.[17,20]

Ceftolozane / tazobactam

Ceftolozane is a novel cephalosporin broad-spectrum which have a similar structure to ceftazidime. Tazobactam is a β-lactamase inhibitor that inhibits β-lactamases, including ESBLs like CTX, SHV, and TEM. Combination of ceftolozane with tazobactam increases the activity of ceftolozane to Enterobacteriaceae producer ESBL, P. aeruginosa, and some anaerobic bacteria which multidrug-resistant like *Bacteroides fragilis*.[15-18]

Criteria sensitivity ceftolozane/tazobactam is 2/4 mg/l on Enterobacteriaceae, 4/4 mg/l on P. aeruginosa. Ceftolozan/tazobactam breakpoint 2mg/l in Enterobacteriaceae producer ESBL with inhibiting power 81.8%, *E. coli* producer ESBL 95%, and K. pneumoniae producing ESBL 56.7%. ASPECT-cIAI and ASPECT-cUTI trials showed that ceftolozane/tazobactam was 25.3% more sensitive than levofloxacin and more sensitive by 97.4% compared meropenem.[16-20]

A multicenter retrospective study in Italy from 2016 – 2019 years shows giving an improvement in clinical 83.7% in patients who were infected with Enterobacteriaceae producer β-lactamase, which was treated with ceftolozane/tazobactam.[23]

Nor classified Ceftazidime/avibactam

Ceftazidime – avibactam is a combination of a cephalosporin with non-BLBLI, which is active against Enterobacteriaceae and *P. aeruginosa*, producing β-lactamase class A (ESBL and KPC), β-lactamase class C (AmpCs) and some Enterobacteriaceae produce class D β-lactamase (OXA) but β-lactamase did not show activity against class B carbapenemases.[16,17]

United States Food and Drug Administration 2015 recommends a combination of ceftazidime-avibactam for complicated UTI and intraabdominal infection with a dose of 2 g per 8 hours during 7 days on UTI with complications and 0.5 g 8 hours for 4 to 14 days for uncomplicated UTI. Novel In vitro antibiotics has activity against Enterobacteriaceae, which produce extended-spectrum beta-lactamase, which could be seen in the following table.[16,20]

Table 5. Novel antibiotics activity in vitro to Enterobacteriaceae, which produce extended-spectrum β-lactamase.[16]

Novel antibiotics	This activity vitro
Ceftazidime–avibactam	**ESBL** AmpC *Klebsiella pneumoniae* carbapenemase (KPC) OXA-48 No active oppose metallo-β-lactamase (MBL)
Ceftazidime/avibactam	**ESBL** Methicillin-resistant Staphylococcus aureus AmpC KPC OXA-48
Ceftolozane–tazobactam	**ESBL** some AmpC Multidrug-resistant Pseudomonas aeruginosa
Imipenem-releactam	**ESBL** AmpC KPC OXA-48 Not active oppose MBL
Plazomicin	**ESBL** AmpC KPC OXA VIM

2. Conclusion

Multidrug-resistant (MDR) caused by extended-spectrum resistance beta-lactamase (ESBL) can be detected by phenotyping and genotyping methods. Alternative treatment of MDR ESBLs other than carbapenems can be β-lactam / β-lactamase inhibitor combinations such as piperacillin/tazobactam (PZT).

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