

Review Article

Overview of β -Lactamases and Current Techniques for Detecting Beta-Lactamase Mediated Resistance

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Abstract

Beta-lactam is a major antibiotic group that carries beta-lactam ring in the structure of antibiotics. Beta-lactam antibiotics are divided into 5 basic classes as penicillins, cephalosporins, monobactams, carbapenems and beta-lactamase inhibitors according to the beta-lactam ring side chains and other rings. All beta-lactam antibiotics affect by inhibiting the enzymes (penicillin binding proteins, PBPs) involved in the cross-linking of the peptidoglycan layer of the cell wall, which is depotentiates, and this leads to osmotic rupture. Beta-lactam antibiotics are one of the most common antibacterial agents used in the treatment of both community and hospital-acquired infections. Due to the widespread use of beta-lactam antibiotics, it is observed that bacteria also develop new resistance mechanisms and their resistance to these antibiotics is increasing. Beta-lactamases are the main responsible for resistance to these antibiotics and the failure of beta-lactam antibiotics in treatment. Therefore, beta-lactamase inhibitors have been developed and combined with beta-lactam antibiotics.

These inhibitors are not effective all types of beta-lactamases. In addition, the discovered beta-lactamases are increasing day by day. Characterization of the beta-lactamase type is essential for the detection of the effective antibiotherapy. In this review, the classification of beta-lactamases, the methods used in laboratory detection of beta-lactamases and the current beta-lactamase inhibitors used in treatment will be discussed.

ABBREVIATIONS

6-APA: 6-Aminopenicillanic Acid; EUCAST: The European Committee on Antimicrobial Susceptibility Testing; MBLs: Metallo-Beta-Lactamases; EDTA: Ethylene Diaminetetra Acetic Acid

INTRODUCTION

The history of penicillin, which was the first discovered beta-lactam antibiotic, began with Alexander Fleming [1]. The beta-lactams ring was the common structure in the developed penicillin derivatives. The beta-lactam nucleus, 6-APA proved to be the key in penicillin synthesis and modification. Penicillins, cephalosporins, monobactams, carbapenems are located in the beta-lactam antibiotic group [2].

Beta-lactam antibiotics, whose mechanism of action is inhibition of the last stage of bacterial cell wall synthesis, are the largest family of antimicrobial agents and the most widely used in current clinical practice. Unfortunately, increasing resistance to these antibiotics limits their utility [3]. Mechanisms of resistance to beta-lactams contain the production of efflux pumps, the modification or reduced production of outer membrane porins (in Gram negative bacteria), alterations of Penicillin-Binding Proteins (the molecular target of beta-lactams) and the production of beta-lactamase (an enzyme able to break down beta-lactam ring) [4]. One of the primary mechanisms of bacterial

resistance to beta-lactams is through the production of beta-lactamase enzymes [3].

Beta-lactam/beta-lactamase inhibitor combinations (BLICs), such as piperacillin-tazobactam or amoxicillin-clavulanate, are particularly useful for the treatment of infections caused by organisms that produce beta-lactamases [5,6].

BETA-LACTAMASES

The beta-lactamases breaks the beta-lactam ring and makes the antibiotic inactive before it reaches the PBP target. Initially beta-lactamases were intended by the name of the strain or plasmid that produced them, an example that persists in such enzyme names as PC1 or P99. In 1975, the application of isoelectric focusing for beta-lactamase characterization allowed many more enzymes to be differentiated [7-9].

The characterization and classification of beta lactamases were facilitated by the use of DNA sequencing. While plasmid mediated enzymes are generally expressed in Gram-negative organisms basically, chromosomally located inducible expression of beta-lactamases is also extensive [10,11].

Beta-lactamases are evaluated by two basic classifications [12]. The molecular classification proposed by Ambler (in 1980 suggests four distinct molecular classes: A, B, C and D based on the amino acid sequencing and the conserved motifs [13]. Although classes A, C and D enzymes utilize serine for beta-

lactam hydrolysis, class B metalloenzymes that require divalent zinc ions (metal ion) for substrate hydrolysis [10].

The second scheme is named as Bush, Jacoby, and Medeiros functional classification, which groups different beta-lactamases according to their substrate and inhibitor profiles, was first attempted in 1989 and then improved in 1995. This method correlates the beta-lactamases with phenotypes in clinical isolates [13]. Based on the differences among the enzymes in these groups, they were further divided into several subgroups [14]. The three major groups of enzymes are described by their substrate and inhibitor profiles: group 1 cephalosporinases that are not well inhibited by clavulanic acid; group 2 penicillinases, cephalosporinases and broad spectrum beta-lactamases that are generally inhibited by active site-directed beta-lactamase inhibitors; and the group 3 metallo-beta-lactamases (MBLs) that hydrolyze penicillins, cephalosporins and carbapenems and that are poorly inhibited by almost all beta-lactam-containing molecules [14,15].

Group 1 Cephalosporinase

Group 1 enzymes are cephalosporinases belonging to molecular class C. AmpC enzymes encoded by both chromosomal and plasmid genes are also evolving to hydrolyze broad-spectrum cephalosporins more efficiently. Transmissible plasmids have acquired genes for AmpC enzymes, hence transferable between species. These enzymes appeared in Enterobacteriaceae that lack chromosomal AmpC enzymes (*Proteus mirabilis*, *Salmonella* spp. and *Klebsiella* spp) or only express low basal level of AmpC like *Escherichia coli* and *Shigella* spp [16].

AmpC beta-lactamases are active on penicillins but even more active on cephalosporins and can hydrolyze cephamycins such as cefoxitin and cefotetan; oxyiminocephalosporins such as ceftazidime, cefotaxime, and ceftriaxone. They are usually resistant to inhibition by clavulanic acid [15]. They have a high affinity for aztreonam, in contrast to the class A cephalosporinases [17].

AmpC beta-lactamases encoded by chromosomal are expressed principally at very low grades. These enzymes generally do not paytake to beta-lactam resistance, but in some organisms (*Serratia marcescens*, *Citrobacter freundii*, *Morganella morganii*, *Providencia stuartii* and especially *Enterobacter cloacae*) they can be provoked under certain situations such as the existence of a beta-lactam [as amoxicillin, ampicillin, imipenem, and clavulanic acid]. The indicible enzymes cause clinical resistance and failure of treatment [18].

Group 2 Serine Beta-Lactamases

Functional group 2 beta-lactamases, containing molecular classes A and D, represent the largest group of beta-lactamases, due primarily to the increasing identification of ESBLs [19].

Subgroup 2a: These beta-lactamases represent penicillinase activity. They are the predominant beta-lactamases in Gram-positive cocci. Subgroup 2a beta-lactamases are inhibited by clavulanic acid and tazobactam. These beta-lactamases have insufficient activity on cephalosporins.

Subgroup 2b: Comprises enzymes that hydrolyze penicillin

and early cephalosporin such as cephaloridine and cephalothin, and are strongly inhibited by clavulanic acid and tazobactam. The subgroup 2b contain the TEM-1, TEM-2, and SHV-1 enzymes [19].

Subgroup 2be: Include enzymes that are capable of inactivating third-generation cephalosporins (ceftazidime, cefotaxime, and cefpodoxime) as well as monobactams (aztreonam). Because of their board activity against third generation cephalosporins they are named Extended Spectrum Beta-lactamases (ESBLs). Organisms that produce ESBLs proceed an important reason for therapy failure with cephalosporins and have serious consequences for infection control [20]. Most ESBLs can be divided into three groups: TEM, SHV, and CTX-M types [21].

TEM types ESBLs: TEM-3, originally reported in 1989, was the first TEM-type beta-lactamase that displayed the ESBL phenotype. Although TEM-type beta-lactamases are most often found in *E. coli* and *K. pneumoniae*, they are also found in other species of Gram-negative bacteria with increasing frequency [22].

SHV type ESBLs: Substitutions found in SHV-type derivatives are shown under the amino acids of SHV-1 [22].

- **CTX-M type ESBLs:** Because of its predominant cefotaxime activity and the location of its isolation (Munich) was named CTX-M. These enzymes are not very closely related to TEM or SHV beta-lactamases in that they share only approximately 40% identity with these two commonly isolated beta-lactamases [23]. CTX-M type ESBLs possess extraordinary high hydrolytic activity against cefotaxime than ceftazidime [24]. In addition to the rapid hydrolysis of cefotaxime, another genuine characteristic of these enzymes is that they are inhibited better by the beta-lactamase inhibitor tazobactam than by sulbactam and clavulanat [25].
- **Subgroup 2br:** Broad-spectrum beta-lactamases that have acquired resistance to clavulanic acid
- **Subgroup 2ber:** Contains TEM enzymes that combine an extended spectrum with relative resistance to clavulanic acid inhibition. These group includes TEM-50, which had amino acid substitutions common to both the ESBL and inhibitor-resistant TEMs, was recently identified. This enzyme was resistant to inhibition by clavulanate, but it also conferred a slight resistance to the expanded-spectrum cephalosporins [26].

Subgroup 2c: These beta-lactamases are able to hydrolyze carbenicillin or ticarcillin at least % 60 as rapidly as benzylpenicillin. These penicillinases are generally easily inhibited by clavulanic acid or tazobactam [15].

- **Subgroup 2ce:** Includes the recently named extended-spectrum carbenicillinase RTG-4 (CARB-10) with expanded activity against cefepime and cefpirome [27].
- **Subgroup 2d:** beta-lactamases distinguished by their ability to hydrolyze cloxacillin or oxacillin and thereby are known as OXA enzymes. Many beta-lactamases in this subgroup are inhibited by NaCl.
- **Subgroup 2de:** Are cloxacillin or oxacillin hydrolyzing

enzymes with an extended spectrum that includes oxyimino-beta-lactams but not carbapenems. OXA-11, OXA-14 and OXA-15 beta-lactamases are in this group. They have most often been found in Turkey and France.

- **Subgroup 2df:** 2df beta-lactamases are OXA enzymes with carbapenem-hydrolyzing activities. The OXA-type beta-lactamases confer resistance to ampicillin and cephalothin. They are characterized by their high hydrolytic activity against oxacillin and cloxacillin and the fact that they are poorly inhibited by clavulanic acid. In *Acinetobacter baumannii*, OXA type beta-lactamases are usually produced by genes that are located on the chromosome [28]. However, OXA-23 and OXA-48, which have been identified in Enterobacteriaceae, are acquired by genes on plasmids [29].
- **Subgroup 2e:** Characteristics of the subgroup 2e cephalosporinases include the ability to hydrolyze extended-spectrum cephalosporins and to be inhibited by clavulanic acid or tazobactam. They can be confused with the group 1 AmpC enzymes or with ESBLs because they may appear in similar organisms and with comparable resistance profiles. Subgroup 2e enzymes can be differentiated from AmpC enzymes by their poor affinity for aztreonam [30].

Subgroup 2f: Include serine carbapenemases from ambler class A. Carbapenemases are beta-lactamases that have the activity of hydrolyzing carbapenems. They have the ability to hydrolyze penicillins, cephalosporins, monobactams and carbapenems. This group enzymes can be inhibited better by tazobactam than by clavulanic acid.

The beta-lactamases in which molecular classes A and D have a serine-based hydrolytic mechanism, whereas molecular class B beta-lactamases are all metalloenzymes with an active-site zinc.

The class A serine carbapenemases contain the NMC (for “not metalloenzyme carbapenemase”), IMI (imipenem-hydrolyzing beta-lactamase), SME (for “*Serratia marcescens* enzyme”), GES (Guiana-Extended-Spectrum) and KPC (*Klebsiella pneumoniae* carbapenemase). Of these, SME, NMC and IMI are chromosomally encoded enzymes [31].

KPC and GES are plasmid-encoded group 2f enzymes. The first KPC-producing *K. pneumoniae* isolate was reported in 2001 [32]. Although KPCs are associated with *K. pneumoniae*, this enzyme has also been identified in other several gram negative bacteria [33]. KPCs are encoded by the blaKPC gene that interprets transitions between species. Global spread is largely explained by its location in the Tn3-type transposon, Tn4401 [34]. KPCs may appear to be susceptible to imipenem and meropenem in automated routine susceptibility testing, leading to misdiagnosis and making it difficult to diagnose.

KPC carbapenemases have been associated with outbreaks due to multidrug resistant Gram negative bacterial infection, especially in US [35].

Subgroup 3

This group include MBLs which is also classified in

Ambler class B. MBLs are a group of featured enzymes that can inactivate most commonly used beta-lactam-based antibiotics including carbapenem. They are separated from the other serine carbapenemases by their requirement for zinc ion to be used in their active site. The MBLs have insufficient affinity or hydrolytic capability for monobactams and are not inhibited by clavulanic acid or tazobactam. The MBLs are inhibited by metal ion chelators such as EDTA and dipicolinic acid. The first metallo-beta-lactamases identified and studied were *Bacillus cereus*, *Aeromonas* spp. and *S. maltophilia*, which are chromosomal enzymes found in opportunistic pathogenic bacteria [36]. The most common metallo-beta-lactamase families include the enzymes VIM, IMP, GIM and SIM which are included in the various integron constructs in which they are included as gene cassettes. These integrons can be easily transferred between bacteria by plasmids or transposons [37]. Rapidly spreading antibiotic resistance is a major problem both clinically and epidemiologically. The importance of metallo-beta-lactamases in the rapid spread of resistance has recently increased. The newly identified New Delhi MBL 1 (NDM-1) is a novel member of this family that is capable of hydrolysing a broad variety of clinically important antibiotics [38].

The first bacterial isolate carrying the MBL later designated blaNDM-1 was a *Klebsiella pneumoniae* from a Swedish patient of Indian origin who traveled to New Delhi and acquired a urinary tract infection there [39,40].

The bla-NDM-1 gene was found on a resistance-conferring genetic element that was easily passed on to other Enterobacteriaceae and that implicated a variety of other resistance regions such as containing a gene encoding CMY-4 (a broad-spectrum beta-lactamase) and genes inactivating ciprofloxacin, erythromycin rifampicin, and chloramphenicol. NDM-1 can hydrolyze all beta-lactams except aztreonam. Bacterial infections producing NDM-1 are difficult to treat. There are many antibiotic resistances except polymyxins [39,41].

Subgroup 4

This group contains enzymes that have as yet been incompletely characterized.

DETECTION OF BETA-LACTAMASE-MEDIATED RESISTANCE

Recommended methods for detection of ESBLs in Enterobacteriaceae

It is recommended mandatory to determine the ESBL to take infection precautions in many places. The recommended method for detecting ESBL-producing Enterobacteriaceae is based on non-susceptibility to indicator oxyimino-cephalosporins, followed by the application of phenotypic tests. Broth dilution, agar dilution, disk diffusion or an automated system can be used for ESBL-screening in Enterobacteriaceae. It is needed that both cefotaxime (or ceftriaxone) and ceftazidime are used as indicator cephalosporins.

Phenotypic confirmation methods

The common phenotypic methods are the combination disk test (CDT), the double-disk synergy test (DDST), the ESBL

gradient test, and the broth microdilution test that based on the in vitro inhibition of ESBL activity by clavulanic acid are recommended for ESBL confirmation [20,42].

Combination disk test (CDT): The basis of this method is to evaluate the inhibition zone around a disk of cephalosporin and around a disk of the same cephalosporin plus clavulanate. The test is positive if the inhibition zone diameter is ≥ 5 mm larger with clavulanic acid than without [43].

Double-disk synergy test (DDST): Disks containing cephalosporins (cefotaxime, ceftazidime, cefepime; each of them 30 μ g) are applied to medium either side of one containing clavulanic acid (amoxicillin-clavulanic acid; containing 10 μ g of clavulanate) positioned at a distance of 20 mm (centre to centre). A positive result is indicated when the inhibition zones around any of the cephalosporin disks are augmented or there is a 'keyhole' in the direction of the disk containing clavulanic acid [20].

Gradient test method: ESBL gradient tests have been developed in order to quantify the synergy between extended-spectrum cephalosporins and clavulanate. The test is positive if \geq eightfold (more than three doubling dilution steps) reduction is evaluated in the MIC of the cephalosporin combined with clavulanic acid compared with the MIC of the cephalosporin alone or if a phantom zone or deformed ellipse is present [43]. Interpreting results of the ESBL gradient test strips is delicate and requires training. In addition, ESBL detection by gradient test may fail when the MIC values for cephalosporins fall outside the range of MICs available on the test strip [40].

Broth microdilution: Mueller-Hinton broth containing serial twofold dilutions of cefotaxime, ceftazidime, aztreonam, or cefepime with or without clavulanic acid was prepared. An eightfold or greater decrease in the MIC of any of the cephalosporins in the presence of clavulanic acid was considered a positive result for ESBL.

Indeterminate test results and false-negative test results may result from the overproduction of AmpC beta-lactamases, which mask the occurrence of ESBLs. Phenotypic confirmatory tests based on the detection of cephamycin hydrolysis or AmpC inhibition will distinguish AmpC beta-lactamases from ESBLs. Cefepime (used as indicator cephalosporin) is generally not hydrolyzed by AmpC beta-lactamases. Cefepime may be used in all the CDT, DDST, gradient test or broth dilution test formats. Alternative approach contain use of cloxacillin, which is a good inhibitor of AmpC enzymes [44].

Genotypic confirmation: Conventional polymerase chain reaction (PCR) can be time consuming and exhaustive due to the wide variety of mutations in ESBL-encoding genes. A microarray approach would be of great help in detecting simultaneously several enzyme-encoding genes from a single strain [44].

Recommended methods for detection of carbapenemases in Enterobacteriaceae

Meropenem is the carbapenem which provides the best balance of sensitivity and specificity and thus it is usually preferred in routine susceptibility tests. According to EUCAST methodology [46]; Ertapenem screening cut-off for zone

diameter < 25mm (with 10 μ g disks) and MIC >0,125mg/L, meropenem screening cut-off for zone diameter < 28mm (with 10 μ g disks) and MIC >0,125mg/L. Isolates of reduced sensitivity to carbapenems in routine susceptibility testing; phenotypic methods should be applied to detect carbapenemases.

Combination disk testing: The requirements for the combination disc test method are commercially available from many manufacturers. The disks include meropenem \pm several inhibitors. Class A carbapenemases are inhibited by boronic acid. Class B carbapenemases (MBLs) are inhibited by dipicolinic acid and ethylenediaminetetraacetic acid (EDTA). There are no appropriate inhibitors for OXA-48-like enzymes. OXA-48-like carbapenemase producers exhibit high resistance (>128 mg/L, zone diameter) to temocillin, but this is not specific enough to be a phenotypic marker. The main disadvantage of CDT is that it takes a long time (overnight incubation) [45].

Biochemical (colorimetric) tests: The CarbaNP test will give rise to a pH-change resulting in a colour shift from red to yellow with phenol red solution. The test uses isolated bacterial colonies and is based on in vitro hydrolysis of a carbapenem, imipenem. The advantages of the test are that it is rapid (<2hours) and cheaper than molecular methods [46].

Carbapenem inactivation method: The basis of this method is to determine enzymatic hydrolysis by incubating a carbapenem with a bacterial suspension. The main disadvantages of this technique that the negative predictive value of the test is still not clear and it takes a long time.

Detection of carbapenem hydrolysis with MALDI-TOF

With the use of molecular methods in the field of microbiology, there have been many advances in this area. As one of the important products of these advances that 'matrix-assisted laser desorption / ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been used in recent years to examine microbiological materials [47]. The basis is to determine in a mass spectrometry appliance (MALDI TOF) the decrease or disappearance of definite specific peaks of carbapenems in a mass spectra when a bacterial suspension is in advance incubated with the carbapenem. The method has been demonstrated in various studies to have good sensitivity and specificity [48]. The disadvantage of this technique that optimization and standardization of the MALDI-TOF MS assay are required for each drug-enzyme combination separately. Furthermore, it requires expert knowledge for evaluation because the mass spectrum of each antibiotic is different [49].

Current overview of carbapenemases

The globalemergence of carbapenem-resistant Enterobacteriaceae (CRE) has become a major threat to public health. The Centers for Disease Control and Prevention have recently classified CPE as one of the most urgent antimicrobial-resistance threats. The transmission of CPE occur by plasmids, or transposons from person to person, with such transmission existing predominantly in healthcare institutions. Since KPC was identified in 1996 in the United States, it has emerge rapidly other countries including Italy, Colombia and the United Kingdom. At present, OXA-48 is the most prevalent and is widespread in Klebsiella pneumoniae in Turkey, the Middle-East, North Africa and Europe. On account of

their point mutant analogues with ESBLs, OXA-48-type producers are among the most difficult carbapenemase producers to be characterised. Therefore, their true prevalence rates are difficult to estimate [50].

Since NDM was first reported in India [41], the sequences of 18 NDM variants (NDM-19 unpublished) have been reported. Treatment of bacterial infections with the spread of NDM-producing bacteria around the world is becoming increasingly difficult with antibiotics being ineffective. Unfortunately, very few research on NDM variants focus on animal-derived bacterial isolates. NDM-17 was discovered in an *E. coli* strain isolated from a chicken [51]. Recently, a novel NDM variant, NDM-20, was described in an *Escherichia coli* strain isolated from a swine [52].

The current situation in global antibiotic resistance

The European Antimicrobial Resistance Surveillance Network (EARS-Net) has published its 2017 report with the participation of data from 30 European Union (EU) and European Economic Area (EEA) countries. EARS-Net data for 2017 show that antimicrobial resistance remains a serious threat in Europe. For invasive bacterial infections, prompt treatment with effective antimicrobial agents is especially important and is one of the single most effective interventions to reduce the risk of fatal outcome. For *Escherichia coli* and *Klebsiella pneumoniae*, combined resistance to various antimicrobial groups was frequent, and extended-spectrum beta-lactamase (ESBL) production was extensive. Resistance percentages were mostly higher in *K. pneumoniae* than in *E. coli*. While carbapenem resistance remained rare in *E. coli*, several countries reported carbapenem resistance percentages above 10% for *K. pneumoniae* (Figure 1.1). Carbapenem resistance was also common in *Pseudomonas aeruginosa* and *Acinetobacter* species, and at higher percentages compared with *K. pneumoniae* [53].

DISCUSSION AND CONCLUSION

Antibiotic resistance has reached levels that threaten the whole world. If emergency measures are not put into practice, an increase in infection-related deaths is possible. In order to prevent the spread of resistance and control of infections, countries need to establish urgent action plans and a global surveillance system is needed. In order to reduce the propagation of resistance genes, we should also take steps to control the resistance in animal food-borne reservoirs.

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