A Mini Review On Family: Beta -Lactamase [E.C 3.5.2.6]

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Abstract:

Beta-lactam are the antibiotic agents used to treat a patients with a bacterial infection worldwide, now a days the great threat of usage of antibiotic due to uncontrollable mutation in infectious gram negative and gram positive bacteria to get resistance against strong environmental pressure. More than 2000 beta-lactamases are available with unique amino acid sequence among them the most clinically important beta-lactamases are penicillinase, cephalosporinases, extended spectrum of beta-lactamase(ESBL) and carbapenem hydrolyzing enzyme have potent antibiotic resistant. Many beta-lactamase inhibitor also available with a small significant antibiotic properties like Clavulanic acid, Sulbactam and Tazobactam. In this mini review I tried to compromise the fact about origin, classification, properties, mechanism of action of beta-lactamases and its prevention.

Key words: Beta-lactam, Antibiotics, Gram positive bacteria, Gram negative bacteria. Beta-lactamases, Beta-lactamases Inhibitor, Clavulanic acid, Sulbactam, Tazobactam Penicillinase, ESBL, Carbapenem. Antibiotic resistance.

➢ TOPLINE VIEW OF BETA LACTAMASE

Beta-lactamases are enzymes and Enzyme commission number is E.C 3.5.2.6. produced by bacteria that provide multi resistant to beta-lactam antibiotics[1].

The "β" (beta) refers to the nitrogen's position on the second carbon in the ring. *Lactam* is a portmanteau of *lactone* (from the Latin *lactis*, *milk*, since lactic acid was isolated from soured milk) and *amide*. The suffix -*ase*, indicating an enzyme, is derived from *diastase* (from

the Greek *diastasis*, "separation"), the first enzyme discovered in 1833 by Payen and Persoz [2].

Beta-lactamases are ancient bacterial enzymes. The class B beta-lactamases (the metallo-beta-lactamases) are divided into three subclasses: B1, B2 and B3. Subclasses B1 and B2 are theorized to have evolved about one billion years ago and subclass B3s is theorized to have evolved before the divergence of the Gram-positive and Gram-negative Eubacteria about two billion years ago[3].

Structural classification of protein: [EMBL PDB ID: PF0014]

Class: multi domain protein (alpha and beta)

Fold: beta lactamase and transpeptidase like

Super family: lactamase or D-ala carboxy peptidase

Protein domain: beta lactamase, class A.

➢ ORIGIN,CLASSIFICATION AND PROPRTIES OF BETA-LACTAMASE

Table1:

Bacteria	Characteristic active site	Molecular class	Original beta-lactamase name	Yr of isolation	location	Organism	Reference no
Gram-positive	Serine	Class A	Penicillinase	1942	England	*Staphylococcus aureus*	4,5,6,7
			TEM1	1963	Greece	*Escherichia coli*	4,5,6,8
			SHV1	1972	Unknown	*Klebsiella pneumoniae*	4,5,6,9
			ESBL(SHV-2)	Pre-1983	Germany	*Klebsiella pneumoniae*	4,5,6, 10.

			TEM-30	1991	France(paris)	*Escherichia coli*	4,5,6, 11.
Gram-positive	Metallo(zn^{+2})	Class B	IMP-1	1988	Japan	*Pseudomanas aeruginosa*	4,5,6, 12.
			NDM-1	2006	India(New Delhi)	*Klebsiella pneumoniae*	4,5,6, 13.
Gram-positive	Serine	Class D	OXA	1962	England	*Salmonella enterica serovar Typhimurium, Escherichia colia*	4,5,6, 14,
			KPC-2	1996	USA(North Carolina)	*Klebsiella pneumoniae*	4,5,6, 15.
Gram-negative	serine	Class C	MRI-1	1988	USA (Massachusetts)	*Klebsiella pneumoniae*	16,5,6, 17,18.

Beta-lactamase hydrolysis the fourth atom ring structure known as Beta-lactam hence deactivate their properties, Beta-lactam antibiotics use to treat gram positive and gram negative bacteria, gram negative bacteria secrete Beta-lactamases when its surround in the environment[1]. Protein beta-lactamase has amino acid sequence of 266. Beta-lactamase classified based on their several criterion like molecular mass, resistance against antibiotic, patient name like TEM and mutation in the sequence.

Among them penicillinase is 50kD protein, it is resistance against penicillin by hydrolyzing beta-lactam ring, it was the first beta-lactamase to be identified[22]. Chromosomal mediated AmpC-beta lactamase represent new threat, they confere resistance against 7-alpha-methoxy-cephalosporins such as cefoxitin or cefotetan, in strain with loss of outer membrane porins provide resistance to carbapenems. In extended spectrum beta-lactamase encoded by plasmid [TEM-1(transposable element beta-lactamase) TEM-2 and SHV-1(sulfhydryl variant)] are confer resistance against to penicillin but not to extended spectrum of cephalosporins, ESBL hydrolysis ring of cephalosporins with side chain

oxy-imino group[23]. 90% of Ampicillian resistance in E.coli due to production of TEM-1[24]

Single amino acid substitution at the position 104,164,238, and 240 produce ESBL phenotype, ESBL occurs due to more than one amino acid substitution [25]. SHV-1 shares 68% of its amino acid with TEM-2 and has similar overall structure, ESBL in this family also have amino acid changes at the active site at 238 or 238 and 240, more than 60 SHV known, SHV-5 and SHV-12 are most common [26]. CTX-M beta-lactamases are belongs to class A group these enzyme named for their greatest activity against cefotaxi, these enzyme show 40% identity to TEM and SHV, more than 80 CTX-M are known among them CTX-M15 are most wide spread type in E.coli[27].

OXA beta-lactamases(oxacillinases) are long recognized and less common but plasmid mediated beta-lactamases , it could hydrolyze oxacillin and related to anti-staphyloccal penicillin, 20% sequence homology with other groups this family originated as phenotype rather than genotype for few beta-lactamases for specific hydrolysis profile, OXA-17 greater resistance to cefotaxime and cefepime than its resistance to ceftazidine. Other plasmid mediated ESBL's such as PER, VEB, GES and IBC beta-lactamases they are uncommon and found in limited number. AmpC type of beta-lactamases are isolated from ESBL, they hyper expressed in plasmids[28] .

Carbapenemases are stable AmpC Beta-lactamases and ESBL, these are derived from class A,B,D but not described in class C, carbapenemases resistant are against oxyimino-cephalosporins and cephamycins. Metallo-beta-lactomases are class B variety they are 19 of them found in japan they spread slowly to other countries in far East, metallo- enzymes are structurally differ from other beta-lactamases by require for zinc ion at the active site[33] . VIM(Verona integron-encoded metallo-beta lactamases reported in Italy, 10% diversity in amino acid of VIM family, 15% in IMP family and 70% between VIM and IMP, they have substantial difference in their thermal stabilities and inhibition profiles[29]. KPC(*K. pneumoniae carbapenemase)*are 10 variants KPC-2 to KPC-11, they distinguish by one or two amino acids substitution, they are 45% homology with SEM(Serratia marcescens enzymes) and NMC/IMI(IMIpenem-hydrolysing β-lactamase)enzymes, they are encoded by self transmissible plasmid[30]

CMY are the class C isolated from virulent strain of *Enterobacter aerogenes,* it is carried on plasmid and it is transfissible to other strain[31-32]. NDM-1 [New Delhi metallo-beta- lactamases-1] it is originally described from new Delhi it is wide spread between india and Pakistan through *E.coli* and *K.pneumoniae*. NDM have several properties which share different properties[29].

➢ MECHANISM OF ACTION OF BETA-LACTAMASE:

The cell wall of the bacteria contains complex polymer of polysaccharides and polypeptide like peptidoglycan, which maintain integrity and shape of bacterial cell, polysaccharides contain N-acetyl glucosamine and N-acetyl muramic acid, 5-amino peptide linked with N-muramic acid sugar, this peptides terminates in D-alanyl D-alanine. The β- lactams inhibit the final transpeptidation by forming covalent bond with penicillin- binding proteins that have transpeptidase and carboxypeptidase activities hence preventing formation of the cross links. The final bactericidal action is the inactivation of an inhibitor of autolytic enzymes in the cell wall, which leads to the lysis of the bacteria[19].

Resistance to penicillins and other β-lactams is due to general mechanisms like; inactivation if antibiotic by β-lactamase, modification of target Penicillin – Binding Protein(PBPs), impaired penetration of drug to target PBPs and efflux. B-lactamase production is the most common mechanism of resistance,.These resistant organisms produce Penicillin- Binding Protiens (PBPs) that have low affinity for binding β-lactam antibiotics consequently they are not inhibited except at relatively high drug concentrations. Resistance due to impaired penetration of antibiotic to target PBPs occurs only in gram-negative species because of their impermeable outer cell wall membrane which is absent in gram-positive bacteria. β-lactam antibiotics cross the outer membrane and into enter gram-negative organisms via outer membrane protein channels (porins). Absence of proper channel or down regulation of its production can greatly impair drug entry into the cell. Poor penetration alone is usually not sufficient to confer resistance because enough antibiotic eventually enters the cell to inhibit its growth[20].

Beta-lactamase enzymatic activity can be detected using nitrocefin, a chromogenic cephalosporin substrate which

changes color from yellow to red upon beta-lactamase mediated hydrolysis.

➢ INHIBITORS OF BETA-LACTAMASE:

These are structurally similar with beta-lactam but do not processes anti microbial activity, they bind irreversibly to the catalytic site of susceptible β-lactamases which prevent the hydrolysis of antibiotics. Currently three inhibitor of beta-lactamase they are Clavulanic acid, Sulbactam and Tazobactam. Clavulanic acid is combined with amoxicillin, sulbactam with ampicillin, and tazobactam with piperacillin and are available as fixed dose combinations[21]. Efficiency of piperacillin-tazobactum for treating serious ESBL infection is controversial[33].

➢ CONCLUSION:

Antibiotics are emerging therapeutics from 20th century and till now. In the era of 21st century people among the community has low immunity to words the bacterial infectious like typhoid, cholera, malaria these infections commonly stays in our body during annual seasons to which our immunity react and control infections, when our immunity does not provide significant protection, antibiotics will save life from these life threatening infections, antimicrobial resistance activity of infectious bacteria leads to several challenges to society that threatens our life. So biomedicine production against the amazing evolution of bacteria, self medication and effective treatment is possible when significant research work and project will undertake by the government funding institute, pharmaceutical companies other NGO's take it into practice.

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