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β Lactamases – Production and their role in Polymicrobial infections.

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ABSTRACT: β –Lactamase-producing bacteria are the most important part involved in polymicrobial infection. They show pathogenic activity through the production of beta-lactamase enzyme. This enzyme plays and crucial role in the inactivation of antimicrobial agents including antibiotics. Beta-lactam ring occurs in antibiotics and is responsible for the cell wall lysis of microbes but Beta-lactam producing bacteria can produce beta-lactamase enzyme and this enzyme is responsible to hydrolyze the beta-lactam ring and inactivates the function of antibiotics. Also, these BLPBs help other microbes which are susceptible to an antibiotic. It gives them defense activity and makes them resistant to antimicrobial agents like penicillin or cephalosporin. Both Gram-positive and Gram-negative bacterial strains can produce Beta-lactamase enzymes. Aerobic as well as anaerobic BLPB not only survive in the presence of penicillin therapy but also protect other bacteria like penicillin-susceptible bacteria from antibiotics – Penicillin. Extended-spectrum of beta-lactamases enzyme produced by gram-negative bacteria including mostly known bacteria E-coli, K. pneumonia, and another spp. consisting of Salmonella, Serratia marcescens, Pseudomonas aeruginosa, Proteus sp. Burkholderiacepacia and Enterobacter spp. With the help of plasmids or transposons, ESBL can be transferred from one species to another. Disease-causing bacterial strain ceaselessly showing resistance via gene mutation towards beta-lactam-containing drugs. Nowadays antibiotic sensitive bacterial infections are treated with the drugs AMX & AMX-C giving great efficacy. It is a global need to stop the misuse and spreading of BLPB infection. Some precise types of antibiotics such as penicillanic acid, sulbactam, clavulanic acid, and tazobactam can inactivate the pathogenic function of the beta-lactamase enzyme. These drugs provide stability toward the complex structure beta-lactam and inactivate the enzyme BL by binding through it.

KEYWORDS:β –Lactamases, Antibiotics, BLPB

I. INTRODUCTION

For so long penicillin use to treat bacterial infections but nowadays various strains of bacteria show resistant effects towards antibiotics. The resistance pattern of antibiotics varies from place to place. Mostly knowing penicillin resistance bacterial strains such are Enterobacteriaceae as well as Staphylococcus aureus.[1] The bacterial strain Staphylococcus aureus shows highly resistant effects against penicillin in hospitals and also recovered through BLPB – β–Lactamases – producing bacteria.[2] The plasmid contains the BL enzyme which plays a principal role in the resistant formula with antibiotics. Some susceptible bacteria continuously show the increasing effect of resistance under certain mechanisms combined with beta-lactamase enzyme production. In that aerobic and some facultative microbes including Moraxella catarrhalis, Haemophilus influenza also anaerobic gram-negative bacilli denoted as AGNB which consist of Bacteroides fragilis, Prevotellabivia, Fusobacterium spp, and Prevotella designs are involved.[3] AGNB recovered from various types of mixed infections. Its rate is continuously increasing. Moraxella catarrhalis strains of organism are the type of normal flora present in the oropharynx. This type of pathogen plays harmful effects on immunodeficient patients. BL recovery rate is about 75% in this type of infection produced by the bacteria Moraxella catarrhalis.[4] This infection is a type of polymicrobial it involves aerobic another facultative and an anaerobic microbiome. The group of Bacteroides fragilis is also able to synthesize BL. [5] These belong to AGNB. There are about 262 strains of the group of Bacteroides fragilis recovered from the patients able to cause the production of BL. For this there are 29% of strains accounted for BLPB.[6] Neisseria gonorrhoeae is a harmful pathogen involved in causing infection of urethritis or cervix inflammation and dissemination. These

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organisms are highly resistant in the part of Africa. It reappears in the form of a mix of aerobic and anaerobic bacterial flora in patients of PID known as Pelvic inflammatory disease. [7.8] BL-producing N. gonorrhea strains are also recovered in gynecological infection and obstetrical infection. BLPB contributes a crucial clinical function in the infection. These bacteria act in a pathogenic role to cause infection and are responsible for the production of the enzyme name beta-lactamase (BL) in their surroundings.[9] Not only in the treatment of penicillin but BLPB also shelter other microbes like penicillin-susceptible from penicillin antibiotic through the liberation of BL in the surrounding atmosphere. These results were studied in vitro as well as in vivo. To this evidence, BLPB not only inactivates antibiotic penicillin but also helps to become resistant to those microbes which are susceptible to the antibiotic penicillin.[10] The capacity of BLPB to shelter the penicillin-susceptible microbes was first noted in 1963 and a large number of failed results were obtained during the treatment of patients.[11] The enzyme Beta lactamase synthesized by Gram-negative microbes has an origin of chromosomal or may have the origin of plasmid which appear in the space of the periplasmic of the gram-negative organism.[12] Isolation of BLPB can be done from various types of infection occurring in children or adults. Sometimes they occurred separately and sometimes they presented with normal flora.[13] Harmful impacts of these organisms were studied that became resistant to other bacterial strains with antibiotics. Continuously increasing rate of resistance of BL penicillin-susceptible to Penicillin in the treatment of PID had been observed and use was restricted for this infection. [14.15] β – Lactamases TEM 1 site belongs to enzyme class-A this is encoded with plasmid in gram-negative bacteria. It can hydrolyze various cephalosporins and penicillins but is inactive towards the extended spectrum of cephalosporin. Researchers did the double-blinded study by comparability of penicillin with two drug one is erythromycin and another one is clindamycin.[16] The drug Erythromycin was accepted because it shows satisfying results against Staphylococcus aureus as well as AGNB. Another drug is clindamycin used because of its efficacy against AGNB, GABHS as well as Staphylococcus aureus. [17,18] After the treatment, it was observed that two patients were cured by applying penicillin.[19] Six patients out of fifteen were cured by using an erythromycin drug. But there are fourteen patients were cured out of fifteen throughout the treatment of clindamycin. [20] Out of fifteen two patients needed tonsillectomy who sustain erythromycin and four patients who sustain penicillin needed surgery tonsillectomy. But there is no requirement for tonsillectomy for all patients who are prescribed clindamycin therapy.[21] It was noticed that clindamycin drug is superior to treating the infection as compared to penicillin treatment against beta-lactamase-producing bacteria.[22]

Antibiotic	Clinical cures	Tonsillectomies
Penicillin	2/15	4/15
Erythromycin	6/15	2/15
Clindamycin	14/15	0/15

Table No 1: Comparative Analysis of Antibiotics [23]

Nowadays AMX and AMX-C also give powerful efficacy to treat various infections like lungs infection, sinusitis, ulcer, and otitis media. To decrease the rate of nasopharyngeal pathogens AMX-C grants more efficacy than AMX in the case of S. aureus. S. Pneumonia, Haemophilus spp. Or GABHS.[24]

B –LACTAMASES – PRODUCTION

Gram-positive as well as Gram-negative bacteria are responsible for the production of β – Lactamases enzyme. Mostly knowing strain of bacteria such as Enterobacteriaceae as well as Staphylococcus aureus produces this enzyme. It is the defense activity shown by bacteria against beta-lactam-containing antibiotics for example N. gonorrhea, Moraxella catarrhalis, Haemophilus influenza, and Bacteroides fragilis. According to the study it was observed that Prevotella or Porphyromonas (Pr. Melaninogenica, Porphyromonasgingivalis, Pr. intermedia, and Pr. bivia) are highly observed under the production of BL. [25] This enzyme plays the principal role in hydrolyzing the beta-lactam ring. Because the beta-

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lactam ring is a bactericidal factor that inhibits the synthesis of the cell wall.[26] Aerobic BLPB strain Haemophilus influenza was detected in URTI. About 15% of patients of it are resistant to penicillin. Maximum isolates were recovered from URTI which was able to produce BL. ESBl – (Extended-spectrum of beta-lactamases) produced by gram-negative bacteria including mostly known bacteria E-coli, K. pneumonia, and another spp. consisting of Salmonella, Serratia marcescens, Pseudomonas aeruginosa, Proteus sp. Burkholderiacepacia and Enterobacter spp.[26,27] The ESBL origin was occur due to the mutation caused on the active sites of TEM 1, TEM 2, and SHV 1 of an enzyme. TEM or SHV types give a high yield of ESBL. Which allows hydrolyzed to penicillin, carbapenem, cephalosporin, and monobactam. With the help of plasmids or transposons, ESBL can be transferred from one species to another.

The figure of transposons and integrons encrypt TEM-1, 41 CTX-M-9,42 and VIM-243 b-lactamases are showing. IR encodes for inverted repeats, bla using for b-lactamase gene, dfr use to indicate dihydrofolate of reductase gene, qac gene denoting to quaternary ammonium compounds, delta deletion derivative, intI denote site-specific integrase gene, aad denoting gene of aminoglycosides adenylyl transferase, sul indicating gene dihydropteroate synthetase, ORF decoded open-reading frame, attI showing recombination site, 59be, 59be are base element, aac encoding aminoglycoside acetyltransferase gene, and IS denoted as insertion sequence.[30]

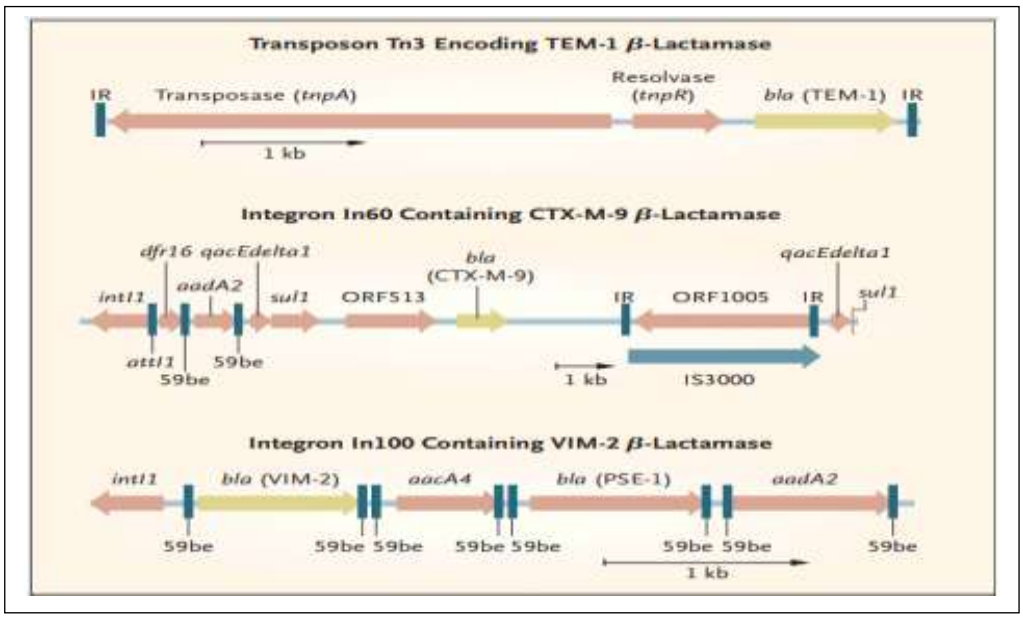

Fig 1: Diagrammatically representation of Genetic Units Encoding Various b -Lactamases.[29]

MODE OF ACTION OF B –LACTAMASES

Antibiotics are the inhibitors for the synthesis of the DNA, and protein synthesis as well as inhibitors for the synthesis of the cell wall. The cell wall of bacteria build up by peptidoglycan. Peptidoglycan provides essential structure to the bacterial cell wall to become sturdy.[31] It has alternate monomers of NAG and NAM (Glycan backbone) linked with β-1, 4 glycosidic bonds. Tetra peptides (amino acids) are only found in monomer NAM. NAM units cross-link one another in the form of L-lys and D-ala.[32] The cross-linking process is catalyzed by the enzyme called transpeptidase enzyme also known as penicillin-binding protein (PBP). This PBP is essential to the recognition of the D-ala – D-ala sequence. If any factor (Like β- lactam antibiotic) interferes with that recognition it will disrupt the synthesis of the cell wall.[33]

The absenteeism of antibiotic therapy enzyme transpeptidase (PBP) enhances crosslinking steps in the adjoining glycan chain. During the cross-linking process, D-alanine can be eliminated as shown in the above figure. GT- Glycotransferases

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appears as an independent subunit or may be integrated with transpeptidase. These generate a covalent bond between the sugar molecules of NAG and NAM. [36] The formation of covalent bonds between peptides and sugar molecules grants a rigid structure to the cell wall and saves the bacterial cell wall from cell rupture by osmotic pressure.[37] The bottom of the Figure shows, Beta-lactam involves the four drugs consisting of Penicillin (Pen), cephalosporin, (Ceph), Monobactum (Mono), and Carbapenem (Carba) which bind to the transpeptidase (PBP) active site, therefore, PBP is not able to form cross-linking of peptidoglycan chain. Ultimately play inhibitory action because bacteria are unable to synthesize a sturdy cell wall.[38] On the other side, the figure shows the Mechanism of MRSA resistance to antibiotics known β-Lactam. β-Lactam consists of an antibiotic that plays a vital role in the permanent inactivation of PBP enzyme to the active site in Drug sensitive bacterial strains.[39] PBP enzyme is very important for the building up of bacterial cell walls. In the antibiotic-sensitive PBP-containing bacteria, the β-Lactam antibiotic inactivates PBP everlastingly as shown at the top of the figure. But at the bottom row, there is a Methicillin-resistant Staphylococcus aureus bacterial strain which antibiotic is antibiotic resistant. This strain expresses PBP2a as an active site that does not permit and block the action of β-Lactam antibiotic to bind the active site, resulting in resistance appearing in a specific manner. [40]

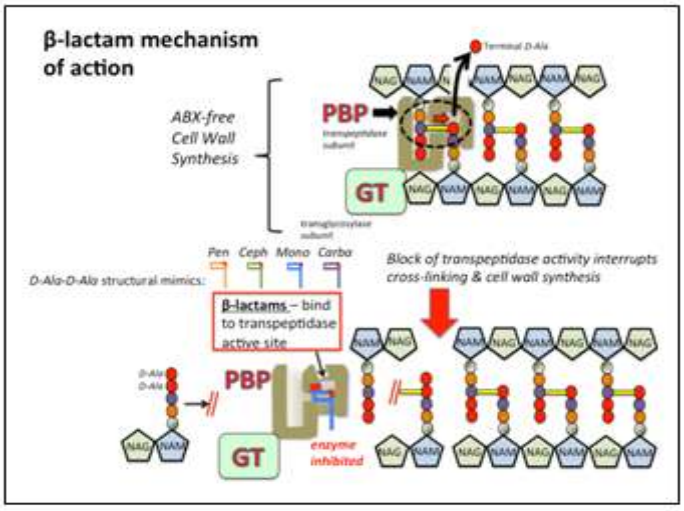

Fig 2: Mode of action of antibiotic- β-Lactam [34]

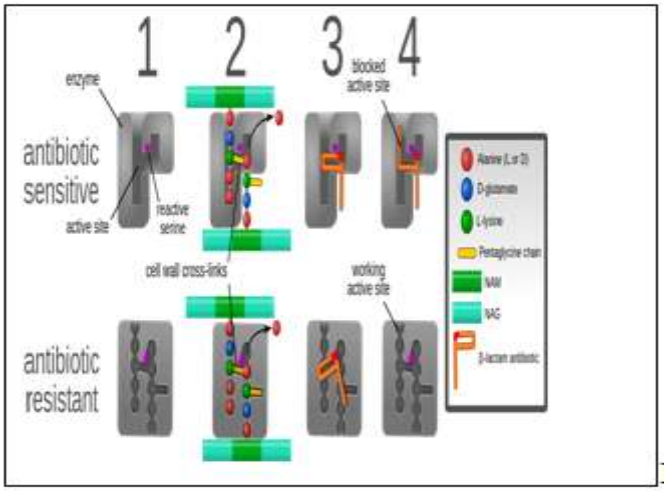

Fig 3: Mechanism of MRSA resistance toβ-Lactam [35]

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ROLE OF B –LACTAMASES IN INFECTION AND TREATMENT

According to the experimental study of in vivo as well as in vitro beta-lactamase enzymes have a powerful impact on polymicrobial infection. The ability of BLPB to shelter penicillin-susceptible microbes was first noted in 1963 including E.coli, Bacillus, Staphylococcus spp, and S. aureus. BL synthesizing AGNB defense Fusobacteriumnecrophorum which is sensitive to penicillin and GABHS – Group-A beta-hemolytic streptococci from penicillin cure in mice.[41] Clindamycin antibiotic or association of penicillin and beta-lactamase inhibitor antibiotic clavulanic acid are most vigorous in contrast to both AGNB as well as GABHS were efficacious in eliminating the infection. Increasing in GABHS resistance to penicillin was noted when co-inoculation was found with S. aureus B. fragilis and Haemophilus parainfluenza. Beta-lactamase occurrence in clinical specimens was recorded in mixed infections and abscesses.[42] These incorporate empyema, abdominal infections, and cerebrospinal specimens, ear infection (acute and chronic). In these cases of infection, there is no use of beta-lactam therapy and the need surgical drain for recovery. Either aerobic or anaerobic inhibits the penicillin activity in the eradication of GABHS tonsillitis and it saves GABHS by BLPB from penicillin through the inhibitions of antibiotic activity.[43] According to the study of Reilly et.al. Beta-lactamase producing bacteria were retrieved in 37 patients out of 50 tonsillitis patients during the treatment of penicillin. By treatment of chemoprophylaxis by using a drug name amoxicillin enhanced the rate of BLPB which recurrence of otitis media in 20 children by about 20 to 100% after six months. The presence of rich BL in saliva ultimately reflects the occurrence of BLPB. Beta lactam-resistant bacterial strains may reappear in the nasopharynx to cause new infections in the ear and sinus. BLPB plays an important role in causing mixed infection.[44] Further reproduction of BL resistance with a b-lactam antibiotic can obtain through another mechanism that consists of the reduction of the entrance of beta-lactam antibiotic via the cell wall of the bacteria. This antibiotic fails to reach the active site where the synthesis of peptidoglycan occurs.[45] Resistance was also found by antibiotics that were unable to bind to the site of penicillin-binding protein in some organisms like Staphylococcus spp., Pseudomonas aeruginosa, Streptococcus pneumoniae, or Neisseria gonorrhoeae. Researcher's study showed that if penicillin-susceptible Bactria or beta-lactam-susceptible bacteria interact with BLPB then these Beta lactam-producing bacteria permitted incompetent response towards cephalosporin as well as penicillin therapy i.e., BLPB secure penicillin and cephalosporin susceptible organisms from penicillin and cephalosporin drug.[46] Beta-lactamase enzyme can be deactivated in the presence of antistaphylococcal penicillin. Some precise types of antibiotics such as penicillanic acid, sulbactam, clavulanic acid, and tazobactam can inactivate the pathogenic function of the beta-lactamase enzyme. These factors provide stability toward the complex structure beta-lactam and inactivate the enzyme BL by binding through it. To these factors, Staphylococcus aureus, Legionella pneumophila, Bacillus strain, M. catarrhalis, H. influenza, E-coli, Bacteroides, Bacillus spp., and Klebsiella pneumonia-produced enzyme BL can be inhibited but these factors are not able to cause same results against chromosome mediated enzyme produced by another Enterobacteriaceae spp. Or against P. aeruginosa. The area where these BLPB were observed included the upper and lower respiratory tracts, within the skin, miscellaneous infections, obstetrics, soft tissue infection, and the inner side of the abdomen. [48]

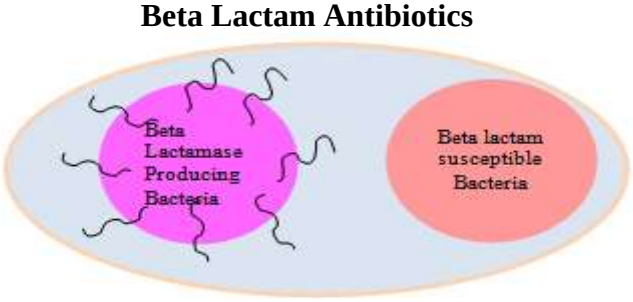

Fig 4: BLPB Protect BLSB from penicillin [47]

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APPLICATION OF B –LACTAM

Antimicrobial Activity

β –Lactam-containing antibiotics are used to treat infections caused by pathogenic microorganisms. [49.50] β –Lactam binds to the active site on PBP and inhibits the synthesis of the bacterium cell wall. ESBL-producing microbes also treated with antibiotics such as penicillanic acid, sulbactam, clavulanic acid, and tazobactam can inactivate the pathogenic role of the beta-lactamase enzyme.[51]

Various Enzyme Inhibitors

Polymorphonuclear cells (PMN) reveal LE- Leukocyte elastase which is mostly neutrophils. LE is a specific serine protease enzyme.[52] LE has the proficiency to diminish certain proteins excluding ECM- the extracellular matrix similarly fibronectin, collagen, and elastin. These caused pathological conditions and damage the organization of ECM.[53] Which consist of rheumatoid arthritis, tumor progression, emphysema, and cystic fibrosis. LE is also involved in the enzymatic base of matrix metalloproteinase (MMP)-9. β –Lactam antibiotic used to inhibit active serine enzyme present in LE. [54,55]

Hypocholesterolemic and Antihyperglycemic Activity

In coronary artery disease (CAD) patients there is essential to maintain fat and cholesterol levels. [56,57 For that drug treatment is widely used to minimize the synthesis of serum cholesterol. β –Lactam tetrasubstituted drugs have been noted for antidiabetic action.[58]

Anticancer Activity

The novel antibiotic coded for β –Lactam based on N-methylation substituting 2-azetidine expressing properties of apoptosis as opposed to the human solid tumor of cell lines namely as breast, head, neck, and prostate. [59,60]

II. CONCLUSION

The above study shows that enhancement of polymicrobial infection is occurred through by giving antimicrobial therapy including aerobic and anaerobic beta-lactamase-producing bacteria. [61,62] This research marks the tonsillitis infection in that BLPB plays a crucial role at the injection site. BLPB inhibits the activity of the beta-lactam ring present in antibiotics by synthesizing the enzyme beta-lactamase. [63,64] Four chemical classes that consist of beta-lactam are penicillin, carbapenem, Monobactam, and cephalosporin become resistant all over the world. Therefore, it is important to prevent the spreading of BLPB within the community. Consumption of β-lactam antibiotic is strictly prohibited in the case of exceedingly resistant category of MIC to prevent harmful mutation. From the study, it has been observed that there is a need of designing advanced and effective β-lactam compounds to treat bacterial infections. [65,66]

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