

# Review on Development and Characterization of Resistance in Nosocomial Bacterial Strains

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**Abstract – Anti-microbial opposition is an issue of expanding occurrence since the mid-1960s and is presently seen as a major risk to clinical practice in the treatment of infectious diseases. Anti-infection safe living beings seem, by all accounts, to be organically fit and are equipped for causing genuine, hazardous infections that are hard to oversee in light of the fact that treatment alternatives are constrained (Mulvey and Simor 2009). The spread of different antimicrobial-safe pathogenic bacteria has been perceived by the World Organization for Animal Health, the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as a genuine global human and creature medical issue. Opposition has been seen to majority of presently affirmed antimicrobial specialists in human and veterinary clinical prescription. This makes the choice of a suitable specialist an undeniably all the more difficult errand. This circumstance has made clinicians increasingly subject to information from in vitro antimicrobial vulnerability testing, and features the significance of the analytic research facility in clinical practice (OIE, 2011). With the disclosure and development of anti-toxins and their medical applications, tranquilize opposition went up against new importance. In this paper we discussed about the studies already done in the field of Nosocomial Bacterial Strains Against  $\beta$ -Lactamase Inhibitor Antibiotics**

## INTRODUCTION

National Committee for Clinical Laboratory Standards (NCCLS) presently called the Clinical and Laboratory Standards Institute (CLSI) gives standard portrayal of antimicrobial testing procedures. Each archive is checked on at regular intervals and either ceased or reexamined. In that way, CLSI models are living archives that are refreshed.

Results of in vitro weakness tests can, best case scenario be utilized as an informed theory to anticipate the restorative result of standard anti-infection dose regimens in typical patients. Numerous factors, for example, pharmacokinetics and pharmacodynamics of medication and medication consequences for bacteria influence the potential clinical viability of a specific anti-microbial.

Alexander Flemming found penicillin from the shape *Penicillium notatum*, which was observed to be dynamic against gram positive bacteria. The accomplishment of penicillin immediately occupied a lot of logical exertion towards the inquiry of different anti-toxins. Selman Waksman found streptomycin and before long pursued by several thousand anti-infection agents. Out of every one of the 50 had a type of clinical use and just a not very many are utilized in the ordinary treatment of infectious diseases (Franklin and

Snow, 2005d). The traditional first-line accessible choices for treating serious infections caused by enterobacteria incorporate penicillins, cephalosporins, monobactams, carbapenems, fluorquinolones, and in specific circumstances, aminoglycosides.

Moreover  $\beta$ -lactam anti-toxins are the most much of the time connected in treatment of bacterial infections.  $\beta$ -lactam anti-microbials all offer the nearness of the  $\beta$ -lactam ring, a four-membered ring in which a carbonyl and a nitrogen are participated in an amide linkage. Subtleties of anti-microbials accessible and sold amid 2012-2016 in India are accounted for beneath.

## REVIEW OF LITERATURE

$\beta$ -lactam anti-toxins display their bactericidal impacts by hindering proteins engaged with cell divider union. The uprightness of the bacterial cell divider is basic to keep up the cell shape in a hypertonic and threatening condition. Osmotic solidness is safeguarded by an unbending cell divider involved exchanging N-acetyl-muramic corrosive (NAM) and N-acetylglucosamine (NAG) units. These glycosidic units are connected by transglycosidases.

A Pentapeptide is joined to each NAM unit, and the cross-connecting of two D-alanine– D-alanine NAM

pentapeptides is catalyzed by PBPs, which go about as transpeptidases. This cross-connecting of adjoining glycan strands gives the inflexibility of the cell divider. The  $\beta$ -lactam ring is sterically like the D-alanine– D-alanine of the NAM pentapeptide, and PBPs "erroneously" utilize the  $\beta$ -lactam as a "building obstruct" amid cell divider blend. This results in acylation of the PBP, which renders the chemical unfit to catalyze further transpeptidation responses. As cell divider union eases back to a stop, constitutive peptidoglycan autolysis proceeds. The breakdown of the murein prompts cell divider trade off and expanded porousness. Therefore, the  $\beta$ -lactam interceded hindrance of transpeptidation causes cell lysis, and the explicit subtleties of penicillin's bactericidal impacts are as yet being disentangled (**Drawz1 and Bonomo 2010**).

Distinctive  $\beta$ -lactams show diverse affinities for the different penicillin restricting proteins and these thus can be corresponded with various morphological impacts. Medications that dilemma most emphatically to penicillin restricting proteins 1a and 1b cause cell lysis at low bacterial fixation. Mixes, for example, cephalosporin, cephalexin tie all the more emphatically to penicillin restricting protein and hinder septation, prompting the arrangement of fibers, which are significantly stretched cells (**Franklin and snow 2015e**).

### Antimicrobial Resistance Mechanisms

Anti-infection agents work by communicating with specific bacterial targets, hindering bacterial cell-divider amalgamation, protein union or nucleic corrosive replication. To achieve this, the anti-toxin must approach and tie to its bacterial target site. Regardless of whether anti-microbial opposition is natural or gained, the hereditary determinants of obstruction encode specific biochemical opposition instruments that may incorporate

1. Enzymatic inactivation of the medication,
2. Alterations to the structure of the anti-infection target site, and
3. Changes that counteract access of a sufficient grouping of the antimicrobial operator to the dynamic site (Neu, 2014 and Koneman et al., 2016)
4. There are four essential systems by which bacteria can defeat  $\beta$ -lactam anti-microbials (Babic et al., 2010)
5. Production of  $\beta$ -lactamase compounds is the most well-known and important instrument of opposition in gram-negative bacteria.

6. Changes in the dynamic site of PBPs can bring down the partiality for  $\beta$ -lactam anti-toxins.
7. Decreased articulation of external layer proteins (OMPs).
8. Efflux siphons, as a major aspect of either an obtained or natural obstruction phenotype, are equipped for trading a wide scope of substrates from the periplasm to the encompassing condition.

### Enzymatic obstruction system

Bacteria may create compounds that change or demolish the chemical structure of an anti-infection, which renders it idle. This component of obstruction is most likely best exemplified by the  $\beta$ -lactamase group of proteins, which act by hydrolyzing the  $\beta$ -lactam ring of penicillins, cephalosporins and carbapenems. There are many  $\beta$ -lactamase compounds that might be recognized by their substrate profiles and exercises. Some  $\beta$ -lactamase qualities are chromosomal, while others are situated on plasmids or transposons. Penicillin obstruction in *S.aureus* and *Neisseria gonorrhoeae*, ampicillin-opposition in *Haemophilus influenzae*, and protection from broadened range Cephalosporins in *E. coli* and in *Enterobacter* species are on the whole ordinarily interceded by the production of  $\beta$ -lactamases. Protection from broadened range Cephalosporins (e.g., Cefotaxime, Ceftriaxone, and Ceftazidime) has emerged principally by 1 of 2 components, the two of which include the production of  $\beta$ -lactamases (**Bradford, 2012**).

### $\beta$ -lactamases

$\beta$ -lactamases ( $\beta$ -lactamhydrolyases, EC 3.5.2.6) are proteins that open the  $\beta$ -lactam ring, inactivating the anti-microbials. Reports on  $\beta$ -lactamases have been expanding in numerous countries.  $\beta$ -lactamases are the fundamental driver of bacterial protection from penicillins and cephalosporins. Complete recognizable proof of these compounds is just conceivable by quality or protein sequencing viewpoints (**Livermore and Brown, 2013**).

$\beta$ -lactamases (ESBL) are compounds that present protection from most  $\beta$ -lactam anti-microbials, including penicillins, cephalosporins, and the monobactam-aztreonam. Network gained ESBL delivering *Enterobacteriaceae* are predominant around the world (**Rodriguez and Jones 2014**).

The main plasmid-intervened  $\beta$ -lactamase in gram-negative bacteria was found in Greece. It was named TEM after the patient from whom it was disconnected (Temoniera). The first  $\beta$ -lactamase protein was distinguished in *Bacillus (Escherichia) coli* before the clinical utilization of penicillin. In a sentinel paper

distributed almost 70 years prior, E. P. Abraham and E. Chain depicted the B.coli as "Penicillinase" (Abraham and Chain 2015).

Expanded range  $\beta$ -lactamases are the compounds with wide substrate specificity to  $\beta$ -lactam antimicrobials and were first distinguished in the year 1983. They are related with expanded bleakness and mortality, particularly among patients on concentrated consideration and high-reliance units in this manner  $\beta$ -lactamases originate before the anti-infection period. The generally acknowledged sub-atomic classification places  $\beta$ -lactamases into four classes: three serine-subordinate protein (classes A, C, and D) and one metal-subordinate (class B) (John et al., 2014).

### **Class A $\beta$ -lactamases**

This is the biggest and best unthinkingly portrayed serine  $\beta$ -lactamase class. Truly, these  $\beta$ -lactamases were depicted as "penicillinases" as their capacity to catalyze penicillin hydrolysis was more prominent than that for cephalosporins. The class A  $\beta$ -lactamases are firmly related in arrangement to low atomic weight class C PBPs, for example, PBP4 of E. coli, H. flu, and Mycobacterium tuberculosis (Massova and Mobashery, 1998). New class A  $\beta$ -lactamases that are dynamic against the later cephalosporins (ceftazidime and cefotaxime and the monobactam aztreonam) and others that are dynamic against the carbapenems are known altogether (additionally with different class C and D compounds) as "extended range  $\beta$ -lactamases" (ESBL) (Bradford, 2012).

### **Class B $\beta$ -lactamases**

These metal-subordinate (quite often divalent zinc)  $\beta$ -lactamases have a wide  $\beta$ -lactam substrate resistance that includes a significant number of the more up to date age cephalosporins, carbapenems, and other  $\beta$ -lactamase inhibitory (clavulanate and penam sulfones)  $\beta$ -lactams important to the treatment of gram-negative contamination (Livermore and Woodford, 2016, Nordmann and Poirel 2012).

This compound was first seen in 1967 by Kawabata and Abraham as chromosomal chemicals of the harmless gram positive Bacillus cereus – an unconstrained freak strain delivering class B  $\beta$ -lactamase constitutively (Walsh and Wright 2015). The structure and elements of metallo  $\beta$ -lactamases have been considered (Concha et al., 2016 and Scrofani et al., 2014).

### **Class C $\beta$ -lactamases**

Class C  $\beta$ -lactamases share with the class A  $\beta$ -lactamases a comparative instruments dynamic site acylation and hydrolytic deacylations for  $\beta$ -lactam hydrolysis. The class C  $\beta$ -lactamases initially named as cephalosporinases because of a substrate inclination for cephalosporins. They are found, with

couple of special cases, in most Gram-negative bacteria and are chromosomally encoded in several living beings (counting Citrobacter freundii, Enterobacter aerogenes, and Enterobacter cloacae) (Rice and Bonomo 2011, Hanson, 2013).

An expanded rate of plasmid-encoded class C  $\beta$ -lactamases was watched 15 years after their first disclosure (Hall and Barlow, 2014). Plasmid-encoded class C proteins have been found in E.coli, Klebsiella pneumoniae, Salmonella spp., C.frendii, Enterobacter aerogenes, and Proteus mirabilis (Bauernfeind et al. 2013, Livermore, 2015, Philippon et al., 2014). Most troubling is that the rate of frequencies of these compounds is most astounding in Klebsiella pneumoniae and E.coli, living beings basic to the healing center and network settings (Rice and Bonomo, 2013).

### **Class D $\beta$ -lactamases**

The class D  $\beta$ -lactamases are progressively experienced among the protective  $\beta$ -lactamase troupe of certain gram-negative pathogens (Hall and Barlow, 2014; and Thomson and Moland, 2014; Nordmann and Poirel, 2012). These  $\beta$ -lactamases were first named as oxacillinases for their capacity to hydrolyze the 5-methyl-3-phenylisoxazole-4-carboxy side chain penicillin class, exemplified by oxacillin and cloxacillin. More than 50 class D OXA variations are presently known (Heritier et al., 2014).

The primary investigations on class D  $\beta$ -lactamases demonstrated that the area collapsing was like serine  $\beta$ -lactamases (Paetzel et al., 2000). Yet, later it was shown that lysine lies in the dynamic site of this class of catalyst (Maveyraud et al., 2012). Class D quality in gram positive bacteria has basic and functional association with Penicillin restricting protein (Colombo et al., 2014).

### **$\beta$ -lactamase inhibitors**

$\beta$ -lactamase inhibitors for the most part hinder ESBL delivering strains.  $\beta$ -lactamase inhibitors, for example, clavulanic corrosive, sulbactam, or tazobactam, are generally recommended in relationship with amino and ureido penicillins for treating gram-negative infections. Clavulanic corrosive, the first  $\beta$ -lactamase inhibitor brought into clinical medication, was disengaged from Streptomyces clavuligerus in the 2015, (Reading and Cole, 2015).

Clavulanate (the salt type of the corrosive in arrangement) demonstrated minimal antimicrobial movement alone, however when joined with amoxicillin, clavulanate altogether brought down the amoxicillin MICs against S. aureus, K. pneumoniae, Proteus mirabilis and E. coli (Brown, 2016). Anyway with the expanded utilization of amoxycylav came

about with protection from them (Guibout et al., 2016).

### Alternation of the Antibiotic Target Site

Anti-toxins must tie to a specific bacterial target site, which changes relying upon the class of anti-infection. An adjustment in the structure of the objective may result in the failure of the anti-infection to tie to its objective. For instance,  $\beta$ -lactam anti-infection agents act by authoritative to structures in the bacterial cell divider called penicillin-restricting proteins. Methicillin-safe strains of *S.aureus* (MRSA) have a hereditary component called staphylococcal tape chromosome mec (SCC mec), which contains the mecA quality that codes for the production of an adjusted penicillin-restricting protein (PBP2a) that does not successfully tie  $\beta$ -lactam anti-microbials. Thus, MRSA is impervious to the majority of the presently accessible penicillins, cephalosporins and carbapenems (Katayama et al., 2015).

### Hereditary Qualities of Antimicrobial Obstruction

Qualities can encode proteins or ribosomal RNA that empowers bacteria to avoid the activities of anti-infection agents. Anti-microbial opposition qualities, be that as it may, are not limited to bacterial genomes. They are likewise much of the time found on versatile hereditary components (plasmids, transposons, and integrons) that promptly pass on a level plane from living being to living being, even crosswise over species limits, consequently bypassing the standard parent-to-descendants course of hereditary stream (Levy and Marshall, 2004). Such anti-infection opposition may either be inherent or gained.

### Inherent Obstruction

Natural obstruction is related with the intrinsic hereditary cosmetics and the life form can be impervious to a specific class of anti-infection agents. This type of obstruction is unsurprising, which makes anti-infection choice straight forward. For instance, all Streptococci are naturally impervious to Aminoglycosides (e.g., gentamicin and tobramycin), and all gram-negative bacilli are inherently impervious to vancomycin.

### Procured opposition

Anti-toxin opposition may likewise be gained. This includes an adjustment in the creature's hereditary synthesis. This may happen by 1 of 2 instruments:

1. Mutation in the bacterial chromosomal DNA, or
2. Mobilization of the hereditary material, for example, plasmids and transposons

Mutations are by and large un-regular occasions, maybe happening at a recurrence of occasion for each 107– 1010 bacteria, however may result in the

development of opposition amid treatment in living beings that are at first defenseless. An important case of this type of opposition is isoniazid obstruction that can happen in *Mycobacterium tuberculosis*. This type of opposition isn't transferable to different living beings. The likelihood of numerous obstruction mutations happening in a solitary life form is equivalent to the result of their individual probabilities. Numerous anti-toxin opposition qualities might be exchanged in the meantime. There are various instances of this type of opposition, including plasmid-interceded production of  $\beta$ -lactamase catalysts, which are fit for inactivating penicillins or cephalosporins in *Staphylococcus aureus*, *Escherichia coli* or *Enterobacter* species (Mulvey and Simor, 2016).

### $\beta$ -Lactamase Genes

$\beta$ -lactamase qualities are commonly situated on huge transferable plasmids that frequently convey other obstruction determinants, for example, those for aminoglycosides, antibiotic medication, sulphonamides and chloramphenicol (Jacoby and Mederios 2012). All enterobacteriaceae can harbor plasmid-intervened ESBL qualities (Bouchillon et al., 2012 and Lautenbach et al., 2013).

$\beta$ -lactamase TEM is observed to be transcendent and extremely lesser measure of blaSHV and blaOXA-1 were accounted for in Enterobacteriaceae. blaTEM and blaSHV qualities were likewise observed to be in blend frame (Colom et al., 2013).  $\beta$ -lactamase qualities groups of blaTEM, blaSHV, blaVEB and blaCTX-M, were accounted for to be exceptionally predominant in numerous nations (Tribuddharat and Fennewald, 2012; Bradford, 2011; Chanawong et al., 2017; Empel et al., 2017).

Plasmid examination of  $\beta$ -lactamase qualities in *Klebsiella pneumoniae* demonstrated that Kp4940 and Kp1 obstruction quality was conveyed by one of two little plasmids with evaluated sizes of 6 and 14 kb, individually. The little size of the Kp1 plasmids recommended that they were not self-transferable, but rather most likely prepared by the 60 kb plasmid (Laksania et al., 2014). Assembly of ESBL qualities in condition prompted the ascent of blaCTX family compound in Enterobacteriaceae (Bonnet, 2014).

Sub-atomic methods, especially PCR, are broadly utilized for affirmation and assurance of  $\beta$ -lactamase qualities, in spite of the fact that there are a few impediments as there are a lot more  $\beta$ -lactamase qualities than blaTEM, blaSHV, blaVEB and blaCTX-M families. blaTEM hyperproduction is a much of the time depicted system by which protection from the  $\beta$ -lactam and  $\beta$ -lactamase inhibitor blends is interceded in *E. coli*. Protection from aminoglycosides is frequently presented by plasmid-encoded blaTEM-type  $\beta$ -lactamase production (Nicolaschanoine, 2017).

### **β-lactamase TEM quality**

TEM and SHV-determined expanded range β-lactamase qualities delivering enterobacteriaceae had been accounted for from all through the world, yet there has been restricted information for the atomic portrayal of these compounds (Tash and Bahar, 2015). Zeba et al. (2014) had revealed that β-lactamases bla SHV quality might be normal among Klebsiella spp and E.coli species. Klebsiella pneumoniae strain BDK0419 contained a transferable plasmid with a sub-atomic size 21 kbp that conveys both blaSHV-2a and blaCTX-M-54 β-lactamase qualities, alongside two different plasmids. The blaCTX-M-54 quality was flanked upstream by an ISEcp1 inclusion succession and downstream by an IS903-like component (Bae et al., 2016).

### **β-lactamase SHV quality**

SHV type β-lactamases can be effectively identified utilizing PCR and liquefying bend investigation in which compounds of about 32 clinical confines can be recognized inside 60 minutes (Randegger and Hachiler, 2011). LCR composing allowed for the definition the SHV families with effortlessness and dependability and can be connected to the point by point portrayal and atomic the study of disease transmission of SHV type β-lactamases (Kim and Lee, 2012).

### **Mutations in β-lactamase qualities**

Mutations in qualities that encode protection from β-lactam anti-infection agents were depicted in various examinations (Jacoby and Sutton, 2014), which generally incorporate mutations in blaTEM at position 21,164 and 265. These mutations might be related with either increment or decline in β-lactam opposition (Stobberingh, et al., 2015).

A considerable number of blaTEM was related with mutations with nonattendance of a section of 136 base sets found upstream the advertiser district including the - 35 locale and not the - 10 area of the advertiser. This finding was related with expanded protection from cefaclor when contrasted with the ordinary secludes. What's more 3.9% of segregates conveyed the bla Rob quality (Molina et al., 2013). Single nucleotide specific PCR was utilized to segregate the polymorphic nucleotides at positions 32 and 317 of the blaTEM qualities from an accumulation of TEM-positive strains (Tristram et al., 2015).

As per the amino corrosive grouping, SHV β-lactamases in Taiwan were fundamentally gotten through stepwise transformation from SHV-1 or SHV-11 and further subdivided by four courses. The stepwise mutations initiated from SHV-1 or SHV-11 to SHV-2, SHV-5, and SHV-12 contain the transformative change in charge of broadened range β-lactamase (ESBL) production in Taiwan (Chang et al., 2011).

### **Antimicrobial Resistance Issues**

(Slama, 2016), Antimicrobial obstruction is presently perceived as an undeniably global issue, both in gram constructive and gram-adverse bacteria For instance, Methicillin safe Staphylococcus aureus (MRSA) slaughtered 19,000 individuals in US consistently, which surpassed the demise caused by some other infectious diseases. Penicillin safe pneumoniae and vancomycin safe Enterococci (VRE) are all the more oftentimes implicated from many industrialized nations compelling regular changes and proposals of the executives of diseases caused by these bugs (Vashishtha, 2010), Appropriate utilization of antimicrobials may prompt a possible, yet adequate, decline in viability, though abuse or abuse would prompt an improper or unsuitable loss of viability and the general public is antagonistically influenced. There are many testing errands in helplessness testing. Helplessness breakpoints change starting with one area of the world then onto the next. In North America, most fluoroquinolones are commonly dosed 250 to 750mg one to multiple times day by day, while in Japan these medications are regularly dosed 100 to 200mg a few times day by day. This distinction in dosing would propose a higher North American weakness break point contrasted with that in Japan. Such provincial contrasts in powerlessness breakpoints can influence correlations between nations.

### **CONCLUSION**

Cyclic sulphonamides have been appeared to be exceptionally valuable heterocycles in restorative science .The sulphonamide group, notwithstanding its antibacterial movement, indicates intense enemy of HIV and dormant leishmanicidal exercises N-sulphonyl β-lactams have been analyzed for their organic properties. the N-sulphonyl monocyclic β-lactams and tried them against a few bacteria. As of late, it has been accounted for that monocyclic β-lactams have novel natural exercises, for example, cytomegalovirus protease inhibitors, thrombin and trypsin inhibitors, cholesterol retention inhibitors ,human leukocyte elastase (HLE) inhibitors ,porcine pancreatic elastase (PPE) inhibitors and anticancer exercises .Besides their organic exercises, the importance of β-lactams as synthetic intermediates has been generally perceived in natural union for instance in the semisynthesis of Taxol Mehta et al,(2013) incorporated azetidinone subsidiaries of the type from azomethine of Dapsone that ended up being a strong antimicrobial medication.

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