Chapter 2
Review of Literature
2.1. Mechanism of Action: Common Drugs

Antibacterial antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity. Most target bacterial functions or growth processes (Calderon CB, 2007).

Antibiotic action mechanism directly relates to target structures affected in bacteria among which cell wall, cytoplasmic membrane, protein biosynthesis, DNA synthesis, RNA synthesis and intermediary metabolism pathways form chief targets (Calvo J, 2009; Hooper DC, 2001).

Figure 2.1: Chief bacterial targets for antibiotics
2.1.1. Targeting Bacterial Cell Wall

Cell wall being exclusive to bacteria is subjected to exploitation at various stages by antibiotic drugs. Antibiotics combat bacteria by targeting bacterial cell wall at three phases, a) Stages of cell wall synthesis b) Altering the pre-requisites of cell wall synthesis and c) Direct damages to structural fabrication of cell wall (Hooper DC, 2001). Absence of its counterpart in Humans makes cell wall an appealing drug target.

**β-lactams:** Success of β-lactam antibiotics instancing penicillin and cephalosporin lie in their action mechanism for inactivation of cell wall assembling enzymes called Penicillin Binding Proteins (PBPs) (Wilke MS, 2005). These antibiotics have impressive efficacy, less cost, low side effects as well as easy delivery.

**Glycopeptides:** Glycopeptide antibiotics like Vancomycin and Teicoplanin alter later stages of peptidoglycan synthesis. Bacterial cell wall structure has a unique (L-aa-D-aa-D-aa) figuration making it scapegoat for specifically toxic antibiotics like glycopeptides. Glycopeptides react with these specific sequences through hydrolysis forming stable complexes which in turn inhibits formation of mature glycan backbone chains. Thus from the basic subunits extruded by cytoplasmic membranes, further transpeptidation reaction meant for imparting rigidity to cell wall is aborted through steric hindrance thus (Reynolds PE, 1989). Among four glycopeptide antibiotics present, currently only vancomycin and teicoplanin are in current use against Gram-positive microorganisms (van Hoek AH, 2011).

**Fosfomycin:** UDP-N-acetylglucosamine enol pyruvl transferase(also known as MurA) catalyzes ligation of phosphoenolpyruvate to 3'-hydroxyl group of UDP-N-acetylglucosamine producing the pyruvate moiety. Glycan and peptide get abridged through this mentioned peptide moiety in peptidoglycan layer (Brown ED, 1995). Fosfomycin is a bactericidal inhibiting peptidoglycan biosynthesis through inactivation of MurA alkylating Cys^{115} residue in its active site (Eschenburg S, 2004).
**Carbapenams:** Carbapenams belonging to β-lactams group, have lower penetrating capacity than penicillin’s, enters gram negative cells through outer membrane proteins (Porins) further traversing periplasmic space. Carbapenams permanently acetylate PBPs inhibiting cell wall synthesis. Through its mechanism of inactivating peptidase domain of PBPs, it blocks all peptidase involving reactions including inhibition of peptide cross linking. Carbapenams differ from penicillin and cephalosporins by a methylene replacement for the sulfur in the 5-membered ring structure (Papp-Wallace KM, 2011).

**Polypeptides:** Isoprenyl pyrophosphate is dedicated to bacterial cell wall synthesis hauling the building blocks of peptidoglycan to exterior of the inner membranes. Bacitracin, a polypeptide antibiotic inhibits C55-isoprenyl pyrophosphate molecule by enzymatic dephosphorylation restricting transport of bacterial metabolic precursors (Stone KJ, 1971).

2.1.2. **Cytoplasmic Disruption**

**Lipopeptide antibiotics:** Daptomycin, a cyclic lipopeptide antibiotic possesses exceptional mechanism of action leading to destruction of membrane potential. Bactericidal action involves insertion of lipophilic daptomycin tail into the bacterial cell membrane causing rapid depolarization alongside generation of potassium ion efflux later restricting formation of DNA, RNA and proteins (Judith N, 2005). Mechanism of action is not yet sufficiently defined (Jared A, 2001). Alternate mechanism of inhibition of lipoteichoic acid synthesis is also suggested (Canepari P, 2990).

**Polymyxins:** Detergent-like antibiotics polymyxins interact with outer membrane lipopolysaccharides (LPS) in which polycationic peptide rings of polymyxins bind with outer membrane displacing calcium and magnesium. These calcium and magnesium bridges are dedicated in maintaining the stability of LPS. Fatty acid side chains further interacts with the LPS, contributing to the insertion of polymyxins into the outer membrane altering its permeability. Affected membranes develop brief cracks approving entry of various molecules including the peptide itself leading to cell death (Zavascki AP, 2007).
2.1.3. Targeting Bacterial Protein Biosynthesis

Bacterial protein biogenesis can be targeted by inhibiting activation of translation, initiation process, binding of the tRNA amino acid complex to ribosomes and elongation process (Calvo J, 2009; Hooper DC, 2001).

Mupirocin: It inhibits synthesis of bacterial RNA and proteins by blocking bacterial isoleucyl-tRNA synthetase, halting incorporation of isoleucine to bacterial proteins (Thomas DG, 1999).

Oxazolidonones: Synthetic antibacterial lincomide of Oxazolidinone group reversibly binds with binding sites on ribosome and particularly inhibits formation of 70S-initiation complex. It binds to sites on 23S rRNA of 50S subunit preventing formation of a functional 70S initiation complex. Translation process of protein biogenesis is hence curbed (Stevens DL, 2004).

Chloramphenicol: Chloramphenicol irreversibly binds L16 protein of 50S subunit of bacterial ribosome’s inhibiting transfer of amino acids to growing peptide chains. Thus peptidyl transferase activity of ribosomes is prevented curbing peptide bond formation and consequent protein production (Jardetzky O, 1963).

Aminoglycosides: Aminoglycosides through binding with 30S ribosomal subunit inhibit translocation of the peptidyl-tRNA from the A-site to the P-site causing misreading of mRNA. This curbs bacterial growth leaving it unable to synthesize proteins (Davis BD, 1988).

Action of MLS antibiotics: MLS group of antibiotics comprise Macrolide-Lincosamide-Streptogramin-B with same mechanism of action related to 50S ribosomal subunit targeted binding yet distinct chemical structure. A singleton set of MLS antibiotics came into existence attributed to same antimicrobial spectra (Ungureanu V, 2010). Hypothesis claims that these antibiotics block the path of exit for nascent peptides causing
dissociation of peptidyl-tRNA from the ribosome. Different antibiotics like macrolides (erythromycin, josamycin, spiramycin and telithromycin, clarithromycin), lincosamide (clindamycin) and streptogramin B (pristinamycin IA) demonstrate the same dissociation function (Tenson T, 2003).

- **Macrolides:** Inhibition of bacterial protein biosynthesis is mediated by binding reversibly to the subunit 50S of the bacterial ribosome, thereby inhibiting translocation of peptidyltRNA. Macrolides prevent peptidyltransferase from adding the peptidyl attached to tRNA to next aminoacid. As well the ribosomal translocation is inhibited through irreversible binding of macrolides to subunit 50S of the bacterial ribosome (Tenson T, 2003).

- **Lincosamides:** Lincosamides prevent bacterial replication by interfering with the synthesis of proteins. They bind to the 23s portion of the 50S subunit of bacterial ribosomes and cause premature dissociation of the peptidyl-tRNA from the ribosome (Leclercq R, 2002).

**Tetracyclines:** Tetracyclines reversibly binds with 16S region of 30S ribosomal subunit prevents the amino-acyl tRNA from binding to mRNA-ribosome complex (Chopra I, 2001).

**Streptothricin:** Via direct ribosomal binding Streptothricins inhibit protein synthesis. These consist of gulosamine, streptolidin and β-lysine moieties (Tschäpe H, 1984).

### 2.1.4. Targeting DNA and Bacterial Replication

The metabolism of nucleic acids can be altered at the DNA-dependent RNA polymerase or in the process of DNA coiling; some compounds affect DNA directly (nitroimidazoles, nitrofurans) (Calvo J, 2009; Hooper DC, 2001).

**Quinolone antibiotics:** Quinolones inhibit topoisomerase II particularly the ligase domain leaving two nuclease domains intact. This alteration coupled with continuous action of topoisomerase II in bacterial cell leads to DNA fragmentation due nuclease activity of intact enzyme domains resulting into cell death (Smith JT, 1986).
Quinolone-gyrase-DNA complexes have also been shown to block the passage of RNA polymerase and to leading to premature termination of transcription in an in vitro transcription system (Willmott CJ, 1994).

### 2.1.5. Affecting Metabolic Pathways

Trimethoprim, Sulphonamides and Sulfamides are candidates of antimicrobial agents that block bacterial metabolic pathways (Calvo J, 2009; Hooper DC, 2001).

**Trimethoprim:** Trimethoprim, a structural analog of folic acid is the last truly introduced novel synthetic antibiotic drug that has been in use since 1962. Trimethoprim through competitive binding with active site of enzyme dihydrofolate reductase (DHFR) inhibits it. DHFR is dedicated in catalysis of NAHPH-dependent reduction of dihydrofolate acid to the active co-enzyme tetrahydrofolate. DHFR like DHPS is a component of folic acid producing biosynthetic pathway (van Hoek AH, 2011; Grape M, 2006).

**Sulphonamides:** Success behind the action mechanism of Sulphonamides is its analogy with $p$-aminobenzoic acid (PABA) involved in folic acid producing biosynthetic pathway. Sulphonamides competitively inhibit enzyme dihydropteroate synthase (DHPS) required for following folic acid synthesis. Consecutive step for thymine production in biosynthetic pathway thus discontinues in-turn curbing bacterial cell growth (Roberts MC, 2002).

### Table 2.1: list of some chief antibiotics classes and their examples (Robert Berkow, 1999)

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Tobramycin, Paromomycin, Spectinomycin</td>
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<tr>
<td>Glycopeptides</td>
<td>Teicoplanin, Vancomycin, Telavancin</td>
</tr>
<tr>
<td>Lipopeptide</td>
<td>Daptomycin</td>
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<tr>
<td>Class</td>
<td>Examples</td>
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<td>---------------</td>
<td>--------------------------------------------------------------------------</td>
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<tr>
<td>Macrolides</td>
<td>Azithromycin, Clarithromycin, Diritromycin, Erythromycin, Roxithromycin, Troleandomycin, Telithromycin, Spiramycin</td>
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<td>Oxazolidiones</td>
<td>Linezolid, Posizolid, Radezolid, Torezolid</td>
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<td>Polypeptides</td>
<td>Bacitracin, Colistin, Polymyxin B</td>
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<tr>
<td>Quinolones</td>
<td>Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Trovafloxacin, Grepafloxacin, Sparfloxacin, Temafloxacin</td>
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<tr>
<td>Sulphonamides</td>
<td>Mafenide, Sulfacetamide, Sulfadiazine, Silver sulfadiazine, Sulfadimethoxine, Sulfamethizole, Sulfamethoxazole, Sulfanilimide (archaic), Sulfasalazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-SMX), Sulfonamidochrysoidine (archaic)</td>
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<tr>
<td>Tetracyclines</td>
<td>Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, Tetracycline</td>
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<tr>
<td>Penicillins</td>
<td>Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacin, Fluclxacin, Mezlocillin, Methicillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin, Penicillin G, Temocillin, Ticarcillin</td>
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<tr>
<td>Carbapenams</td>
<td>Ertapenem, Doripenem, Imipenem/Cilastatin, Meropenem</td>
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<tr>
<td>Cephalosporins</td>
<td>Cefadroxil, Cefazolin, Cefalotin or Cefalothin, Cefalexin</td>
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<td>(Generation 1)</td>
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<tr>
<td>Cephalosporins</td>
<td>Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime</td>
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<td>(Generation 2)</td>
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<td>Cephalosporins</td>
<td>Ceftarolinefosamil, Ceftobiprole</td>
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[Image: Chemical structures of various antibiotics including Sulfonamide Core, Bacitracin, Mupirocin, 2-oxazolidone, Linozolid, Amikacin, Streptomycin, Chloramphenicol, and Penicillin]
Figure 2.2: Structures/ Core structures of various antibiotics
2.2. Multi Drug Resistance

"Drug resistance develops naturally, but careless practices in drug supply and use are hastening it unnecessarily." - Center for Global Development

Since the initial use of antimicrobials, humankind chronologically witnessed an up surge and an acceleration of resistance in bacteria specifically in past decade. Prior to introduction of antimicrobials, extremely low level of antimicrobial resistance genes existed. Selective pressure exerted by antimicrobials and exposure of microbes to humans, their companions and food animals, fishes are other factors responsible for multiple drug tolerance in bacteria (PM Hawkey, 2008). This resulted into selection of bacteria resistant to numerous drugs. Drug resistance along with selective effect is directly allied with usage of antimicrobials (Livermore DM, 2006; PM Hawkey, 2008).

Accumulation of genes coding for resistance against particular drug on R-plasmid results into multidrug resistance. Such accumulation is chaperoned by mechanisms like transposons, integrons, and ISCR elements. Integrons are flawless assemblers of various antimicrobial resistance genes in R-plasmid providing them with powerful promoter for expression (Ploy MC, 2000). Moreover R plasmids are extremely well maintained and passed from cell to cell in a population, attributed to its property of being self-transmissible (Hiroshi Nikaido, 2009).

2.2.1. Mechanisms of action: Drug Resistance

A few mechanisms of drug resistance are;

i. Efflux mechanism

ii. Enzymatic modifications of antimicrobials.

iii. Cleavage or degradation of antimicrobials.

iv. Modification in bacterial cell wall permeability by augmenting mutations in porin genes, limiting antimicrobial access of targets.

v. Alterations of antibiotic targets.

vi. Incorporation of alternate metabolic targets

2.2.1.1. Persister Cells

Pathogenic microorganisms demonstrate persistence in patients after treatment attributed to development of physiological resistance in bacteria without any genetic changes. These are named “Persisters” which are essentially invulnerable. When exposed to antimicrobial agents, these cells do neither die nor grow thus exhibit multidrug tolerance (MDT). Persisters are largely responsible for the recalcitrance of infections caused by bacterial biofilms (Lewis K, 2005).
2.2.1.2. Efflux pumps

Other mechanism for drug resistance is active pumping out of drugs by multidrug efflux pumps. Efflux pumps are the well devised antibiotic resistance mechanisms by bacterial cells accurately expelling out targeted antibiotics. Such mechanisms result into declined concentrations of antibiotics and biocides in bacterial cells increasing their ability to survive against antibiotics (Schindler BD, 2013). Efflux pumps affiliate bacteria with multiple drug resistance given the fact that these pumps can extrude out specific drug or a range of noxious chemicals in surrounding environment (M. A.Webber, 2003). About 5~10% of bacterial genes demonstrate involvement in transport of compounds and expression of efflux pumps tracing ancestral evolutionary origins. Hence efflux pumps are not expressed under any antibiotic stress (Saier M H, 2001; Lomovskaya O, 2001). Prokaryotic efflux pump family types include: The major facilitator superfamily (MFS), The Multi antimicrobial extrusion protein family (MATE), The resistance-nodulation-cell division superfamily (RND), The small multidrug resistance family (SMR) and The ATP-binding cassette superfamily (ABC) utilizing proton motive force as an energy source except the ABC family using ATP hydrolysis to drive the export of substrates (M. A.Webber, 2003). Here RND superfamily pumps from gram negative bacteria are of particular importance as their genes are coded from chromosomes and can be easily overproduced. Results are pumping out of major drug classes (Hiroshi Nikaido, 2009).

Table 2.2: Efflux genes in Staphylococcus aureus, S. epidermidis, S. haemolyticus, S. saprophyticus, S. pneumonia, S. pyogenes, S. agalactiae, K. pneumoniae, S. sonnei, S. flexneri, S. boydii and S. dysenteriae

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<td>active efflux of tetracycline</td>
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<td>2</td>
<td>sepA</td>
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<td>Q5HE37, A6QJ09</td>
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<td>3</td>
<td><strong>norB</strong></td>
<td>Quinolone resistance protein NorB</td>
<td>Multidrug efflux pump conferring resistance against diverse quinolones</td>
<td>A6QGY6, Q2FYJ5</td>
<td>Q2FH03, Q8NWQ5</td>
<td>Q5HYF7, Q6G9C6</td>
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<td>4</td>
<td><strong>mepA</strong></td>
<td>Multidrug export protein MepA</td>
<td>Multidrug efflux for fluoroquinolone antimicrobial agents norfloxacin and ciprofloxacin, tigeglycine resistance.</td>
<td>Q2G140, Q7A7N0</td>
<td>Q5HIW0, Q6GJY2</td>
<td>Q6GCD7, Q8NYB0</td>
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<td>5</td>
<td><strong>norA</strong></td>
<td>Quinolone resistance protein NorA</td>
<td>Efflux of quinolones</td>
<td>P0A0J7, Q5HHX4</td>
<td>Q6GCD7, P0A0J5</td>
<td>Q6GIU7, Q6GBD5</td>
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**Staphylococcus epidermidis**

|   |   |   |   |   |   |   |
|1 | **sepA** | Multidrug resistance efflux pump SepA | Involved in multidrug efflux | Q5HM62 | Q8CRK7 |   |
|2 | **msrA** | Erythromycin resistance ATP-binding protein MsrA | Resistance to streptogramin B and Erythromycin | P23212 |   |   |
|3 | **tet** | Tetracycline resistance protein | Active tetracycline efflux | P62967 |   |   |
### Staphylococcus haemolyticus

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<td>sepA</td>
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<td>mepA</td>
<td>Multidrug export protein</td>
<td>Multidrug efflux protein</td>
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### Staphylococcus saprophyticus

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<td>Multidrug resistance efflux pump</td>
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<td>mepA</td>
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### Streptococcus pneumoniae

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<td>pmrA</td>
<td>Multi-drug resistance efflux pump</td>
<td>Efflux pump for various substrates</td>
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<td>Probable multidrug resistance protein</td>
<td>Multidrug efflux pump</td>
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### Streptococcus pyogenes

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<td>mefA</td>
<td>Macrolide efflux protein A</td>
<td>Resistance to macrolides, streptogramin B and lincosamide</td>
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### Streptococcus agalactiae

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<td>tet</td>
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### Klebsiella pneumoniae

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<td>mdtA</td>
<td>Multidrug resistance protein</td>
<td>Part of a tripartite efflux system composed of MdtA, MdtB and MdtC.</td>
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<table>
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<tr>
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<th>Part of a tripartite efflux system composed of MdtA, MdtB and MdtC.</th>
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<tr>
<th>MdfA</th>
<th>Multidrug transporter MdfA</th>
<th>Efflux pump driven by the proton motive force. Confers resistance to a broad spectrum of chemically unrelated drugs</th>
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### Shigella boydii

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<th>Multidrug resistance protein MdtK</th>
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<tr>
<th>MntP</th>
<th>Probable manganese efflux pump MntP</th>
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### Shigella dysenteriae

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<th>Multidrug resistance protein MdtK</th>
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2.2.1.3. Mechanism of drug resistance to Aminoglycosides

Resistance to aminoglycosides is conferred to bacterial pathogens in multiple ways. Reduced uptake or decreased cell permeability, alterations at the ribosomal binding sites, or production of aminoglycoside modifying enzymes.

Reduced uptake of aminoglycosides confers moderate level resistance to bacterial pathogen and is expected either due to membrane impermeabilization or efflux mechanisms (Mingeot-Leclercq MP, 1989). Modification of 30S ribosomal subunit binding site for aminoglycoside attachment poses as alternate resistance mechanism. This mechanism of resistance is uncommon among aminoglycosides other than streptomycin attributed to their multiple binding capacities over both ribosomal subunits conferring greater resistance (Kucers A, 1997).
Enzymatic modification is major mechanism of aminoglycoside resistance ensuing high level of resistance. Aminoglycoside-modifying enzymes catalyze covalent modification of amino or hydroxyl functions resulting in chemically modified drug with reduced binding affinity to ribosomal binding site (Mingeot-Leclercq MP, 1989).

Aminoglycoside-modifying enzymes N-Acetyltransferases (AAC), O-Adenyltransferases (ANT) and O-Phosphotransferases (APH) are often plasmid encoded but are also linked with transposable elements (Davies J, 1997). N-Acetyltransferases use acetyl-coenzyme A for acetyl CoA-dependent acetylation of an amino group in target, O-Adenyltransferases and O-Phosphotransferases using ATP as donor have an effect on hydroxyl group functions through adenylation and phosphorylation (Mingeot-Leclercq MP, 1989). Further division for aminoglycoside modification proteins are according to specificity of regional difference for modification through enzymes (Kotra, L. P., 2000).

- Four Acetyltransferases: AAC(1), AAC(2), AAC(3), and AAC(6)
- Five Nucleotidyltransferases: ANT(2), ANT(3), ANT(4), ANT(6), and ANT(9)
- Phosphotransferases: APH(2), APH(3), APH(3), APH(4), APH(6), APH(7), and APH(9)
- Bifunctional Enzyme: AAC(6)–APH(2)

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<th>No.</th>
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<th>Mechanism</th>
<th>Genera</th>
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<tr>
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<td>aac(3)-lk</td>
<td>Acetyltransferase</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>2</td>
<td>aac(3)-lla</td>
<td>Acetyltransferase</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>3</td>
<td>aac(6’)-la</td>
<td>Acetyltransferase</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>4</td>
<td>aac(6’)-lb-cr</td>
<td>Acetyltransferase</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>5</td>
<td>aac(6’)-ld</td>
<td>Acetyltransferase</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>6</td>
<td>aac(6’)-lq</td>
<td>Acetyltransferase</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>7</td>
<td>aac(6’)-lla</td>
<td>Acetyltransferase</td>
<td>Klebsiella</td>
</tr>
</tbody>
</table>
### 2.2.1.4. Mechanism of drug resistance to Tetracycline

With the aid of at least three mechanisms pathogenic bacteria acquire tetracycline resistances which include enzymatic inactivation of tetracycline, protection of ribosome using RBP's and energy dependent drug efflux pumps (van Hoek AH, 2011).
Currently 40 different acquired tetracycline resistance markers are identified including 38\textit{tet} for tetracycline resistance, 3\textit{otr}(oxytetracycline resistance) genes; additionally 1 \textit{tcr} gene has been identified.

Table 2.4: Tetracycline resistance genes

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Mechanism</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textit{tet}(A)</td>
<td>Efflux</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>2</td>
<td>\textit{tet}(B)</td>
<td>Efflux</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>3</td>
<td>\textit{tet}(C)</td>
<td>Efflux</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>4</td>
<td>\textit{tet}(D)</td>
<td>Efflux</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>5</td>
<td>\textit{tet}(K)</td>
<td>Efflux</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>6</td>
<td>\textit{tet}(L)</td>
<td>Efflux</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>7</td>
<td>\textit{tet}(M)</td>
<td>Efflux</td>
<td>Streptococcus, Staphylococcus, Klebsiella</td>
</tr>
<tr>
<td>8</td>
<td>\textit{tet}(O)</td>
<td>Ribosomal protection</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>9</td>
<td>\textit{tet}(Q)</td>
<td>Ribosomal protection</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>10</td>
<td>\textit{tet}(T)</td>
<td>Ribosomal protection</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>11</td>
<td>\textit{tet}(U)</td>
<td>Unknown Efflux</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>12</td>
<td>\textit{tet}(W)</td>
<td>Ribosomal protection</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>13</td>
<td>\textit{tet}(32)</td>
<td>Ribosomal protection</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>14</td>
<td>\textit{tet}(38)</td>
<td>Efflux</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>15</td>
<td>\textit{tet}(42)</td>
<td>Efflux</td>
<td>Staphylococcus</td>
</tr>
</tbody>
</table>

2.2.1.5. Mechanism of resistance to β-lactams

Resistance to β-lactam antibiotics poses as a major problem today with ever increasing rates. First ever resistance to penicillin was discovered in \textit{E. coli} by action of enzyme \textit{AmpC} β-lactamase (Abraham EP and Chain E, 1940).

Mechanisms responsible for resistance to β-lactam antibiotics: 1) Distortion of β-lactam rings through hydrolysis, 2) Altered PBPs 3) Efflux and 4) Altered antibiotic permeability (Wilke MS, 2005).
Foundation of all the β-lactam antibiotics involves existence of β-lactam nucleus in their molecular structure. β-lactamases encoded by resistance genes hydrolyze amide linkage of four membered β-lactam rings, distorting antibiotic function. Post expression, β-lactamases are secreted into periplasmic space in gram negative bacteria, bound to cytoplasmic membrane or are released outside in gram positive bacterial species (Weldhagen GF, 2004; Wilke MS, 2005).

Utilizing biochemical structures, β-lactamases were divided into four classes namely: Group 1, 2 and 4 including the serine lactamases and group 3 encompassing metallo-lactamases. Distinction based on molecular features leads to formation of four Ambler classes namely: Ambler classes A, C and D encompass β-lactamases with serine in active site and Ambler class B β-lactamases are all metallo-enzymes active only in presence of Zinc as a cofactor (Ambler, R. P., 1980; Weldhagen GF, 2004).

Ambler classes A, C and D β-lactamases with same folds generate serine nucleophile through deprotonation of active site serine with general base. Nucleophilic attack of the β-lactam ring forms an acyl-enzyme intermediate followed by hydrolysis of the intermediate using a general base activated water molecule.

Presently 1,150 chromosomal, plasmid, and transposon encoded β-lactamases are known (Drawz, S. M., 2010).

PBP mediated antibiotic resistance includes various mechanisms like acquisition of new less sensitive enzyme, mutation of PBPs to lessen interaction with β-lactams or its up regulation (Tajima Y, 2005).

2.2.1.6. Mechanism of resistance to Carbapenams
Resistance mechanisms to carbapenams include inhibition through production of β-lactamases, efflux pumps, mutations altering PBPs and outer membrane proteins structure and/or functions whose combinations confers high level resistance to bacteria (Papp-
Wallace KM, 2011). Currently KPC (Klebsiella pneumoniae carbapenamase) producing Klebsiella, a highly resistant gram negative pathogen is associated with significant morbidity and mortality (Arnold RS, 2011). Treatment of these infections is highly dependent upon tigeclycine and polymyxins. Polymyxins are often only the drugs active against KPC producing K. pneumoniae. Combination of polymyxins and tigeclycine shows no resistance to either drug in treatment cases (Lee J, 2009). There is an increase in gene copy of \( \text{bla}_{\text{KPC}} \) reported for carbapenams resistance in K. pneumonia (Kitchel B, 2010).

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Mechanism</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{blaOXA-181} )</td>
<td>-</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>2</td>
<td>( \text{bla}_{\text{KPC}} )</td>
<td>Hydrolase</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>3</td>
<td>( \text{bla}_{\text{NDM-1}} )</td>
<td>B-Lactamase activity</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>4</td>
<td>ges-1</td>
<td>Acetyltransferase</td>
<td>Klebsiella pneumoniae</td>
</tr>
</tbody>
</table>

2.2.1.7. Mechanism of resistance to Streptothricin

Acetyltransferases through acetylation of Streptothricin producers inactivates them. These AR determinants are plasmid encoded and are easily transferable across bacterial community (Tschäpe H, 1984).

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Mechanism</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{sat}_{2^A} )</td>
<td>Acetyltransferase</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>2</td>
<td>( \text{sat}_{3_A} )</td>
<td>Acetyltransferase</td>
<td>Escherichia</td>
</tr>
<tr>
<td>3</td>
<td>( \text{sat}_{4^A} )</td>
<td>Acetyltransferase</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
</tbody>
</table>

2.2.1.8. Mechanism of resistance to Trimethoprim

Incidentes are unlikely that Trimethoprim being synthetic antimicrobial has any naturally occurring inhibitors. Genes conferring low level resistance to Trimethoprim are
chromosome encoded while genes aiding high level resistance are plasmid encoded. Chromosomal \textit{folA} gene, a non-allelic and drug resistant variant through expression of chromosomal DFHR confers low level resistance to trimethoprim. Within several years of trimethoprim introduction plasmid mediated drug in-susceptible DHFRs emerged in Gram-negative bacteria conferring high level of resistance. Trimethoprim with its capacity to bind with dihydrofolate reductase inhibits reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). DNA synthesis in turn is curbed taking into account THF as main constituent in thymidine synthesis. Lack of THF inhibits bacterial DNA synthesis (van Hoek AH, 2011; Amyes, SGB, 1990; Fleming, MP, 1972; Huovinen P, 1987).

\textbf{Table 2.7: Trimethoprim resistance genes}

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textit{dfrA1}</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>2</td>
<td>\textit{dfrA5}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>3</td>
<td>\textit{dfrA7}</td>
<td>Shigella</td>
</tr>
<tr>
<td>4</td>
<td>\textit{dfrA8}</td>
<td>Shigella</td>
</tr>
<tr>
<td>5</td>
<td>\textit{dfrA10}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>6</td>
<td>\textit{dfrA12}</td>
<td>Klebsiella, Staphylococcus</td>
</tr>
<tr>
<td>7</td>
<td>\textit{dfrA14}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>8</td>
<td>\textit{dfrA15}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>9</td>
<td>\textit{dfrA17}</td>
<td>Klebsiella, Shigella, Staphylococcus</td>
</tr>
<tr>
<td>10</td>
<td>\textit{dfrA18}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>11</td>
<td>\textit{dfrA21}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>12</td>
<td>\textit{dfrA22}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>13</td>
<td>\textit{dfrB1}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>14</td>
<td>\textit{dfrB3}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>15</td>
<td>\textit{dfrB4}</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>16</td>
<td>\textit{dfrD}</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>17</td>
<td>\textit{dfrG}</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>18</td>
<td>\textit{dfrK}</td>
<td>Staphylococcus</td>
</tr>
</tbody>
</table>
2.2.1.9. **Mechanism of resistance to Sulphonamide**

Resistance to sulphonamides is plasmid encoded and mediated by expression of drug insensitive enzyme DHPS. Chromosomal \( \textit{folP} \) gene, a drug resistant variant through expression of chromosomal DFHR confers low level resistance to sulphonamide (Sköld O, 2000). High level resistance is mediated through plasmid encoded genes \( \textit{sul1} \) and \( \textit{sul2} \) characterized in 1980s (Sundström L, 1988).

2.2.1.10. **Mechanism of resistance to fosfomycin**

Three mechanically discriminated yet related genes belonging to glyoxalase family \( \textit{fosA} \), \( \textit{fosB} \) and \( \textit{fosX} \) for fosfomycin resistance are discovered to be encoded both in plasmids and chromosomes. \( \textit{FosA} \) is a Mn(II) and K(+) dependent glutathione transferase. \( \textit{FosB} \) is a Mg(2+) dependent L-cysteine thiol transferase. \( \textit{FosX} \) is a Mn(II)-dependent fosfomycin-specific epoxide hydrolase (Rigsby RE, 2005). A nucleophilic attack over Carbon 1 of epoxide ring in fosfomycin inactivates it (Sharma SV, 2011).

2.2.1.11. **Mechanism of resistance to Quinolones**

Mechanism for quinolone resistance includes: alterations in the targets of quinolones, overexpression of efflux pumps and/or decreased accumulation due to impermeability of the membrane (Ruiz J, 2003).

Resistance to quinolones is both plasmid and chromosome mediated (Martínez-Martínez L, 2008). Chromosome mediated resistance results into reduced membrane impermeability due loss of porin proteins, to over expression of efflux pumps or mutation in target DNA gyrase or topoisomerase II (van Hoek AH, 2011). Mutation in \( \textit{gyrA} \), \( \textit{gyrB} \), \( \textit{parC} \), and \( \textit{pare} \) genes encoding DNA gyrase and topoisomerase II occurring at specific “quinolone resistance determining regions” (Jacoby GA, 2005). First ever plasmid encoded quinolone resistance gene, a \( \textit{qnr} \) determinant coding protective proteins for DNA gyrase and topoisomerase II was first recognized a decade later after plasmid encoded quinolone resistance was suggested (van Hoek AH, 2011).
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Low level of plasmid mediated ciprofloxacin resistance gene, a variant of \( aac(6')-Ib, aac(6')-Ib-cr \). Gene encodes for acetyltransferase called AAC(6')-Ib-crc capable to acetylate ciprofloxacin (Park CH, 2002; Robicsek A, 2006; Strahilevitz J, 2009).

Table 2.8: Quinolone resistance genes

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( qnrA1 )</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>2</td>
<td>( qnrA2 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>3</td>
<td>( qnrB1 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>4</td>
<td>( qnrB2 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>5</td>
<td>( qnrB4 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>6</td>
<td>( qnrB6 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>7</td>
<td>( qnrB7 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>8</td>
<td>( qnrB10 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>9</td>
<td>( qnrB19 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>10</td>
<td>( qnrB20 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>11</td>
<td>( qnrB31 )</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>12</td>
<td>( qnrS1 )</td>
<td>Klebsiella, Shigella</td>
</tr>
</tbody>
</table>

2.2.1.12. Mechanism of resistance to Chloramphenicol

Mechanisms of resistance to chloramphenicol include: decline of membrane permeability, mutations in 50S ribosomal subunit, elaboration of chloramphenicol acetyltransferase, inactivation by phosphor transferases, efflux systems (Schwarz S, 2004). Most frequently occurring mechanism from above is enzymatic inactivation by acetylation of chloramphenicol mediated by diverse range of CAT enzymes (Wright GD, 2005). Chloramphenicol acetyltransferase inactivates chloramphenicol by covalently linking one or two acetyl groups, derived from acetyl-S-coenzyme A, to the hydroxyl groups on the chloramphenicol molecule. Two defined types of genes are responsible for encoding acetyltransferases the classical \( catA \) determinants and the novel, also known as xenobiotic CATs, encoded by \( catB \) variants (van Hoek AH, 2011). Presence of chloramphenicol resistance genes on mobile genetic elements ensure spread of its
resistance even in the absence of a selective pressure. Flourinated derivative of Chloramphenicol, florfenicol (Ff) is also a potent inhibitor of bacterial protein biogenesis (Schwarz S, 2004). Efflux mechanisms are mediated by $cmlA$ and $floR$ genes (Briggs CE, 1999).

### Table 2.9: Chloramphenicol resistance genes

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene</th>
<th>Mechanism</th>
<th>Genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>catA1</td>
<td>Inactivating Enzyme</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>2</td>
<td>catA3</td>
<td>Inactivating Enzyme</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>3</td>
<td>catB2</td>
<td>Inactivating Enzyme</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>4</td>
<td>cat(pC221)</td>
<td>Inactivating Enzyme</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>5</td>
<td>cat(pC223)</td>
<td>Inactivating Enzyme</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>6</td>
<td>cat(pC194)</td>
<td>Inactivating Enzyme</td>
<td>Streptococcus, Staphylococcus</td>
</tr>
<tr>
<td>7</td>
<td>catS</td>
<td>Inactivating Enzyme</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>8</td>
<td>catQ</td>
<td>Inactivating Enzyme</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>9</td>
<td>catB3</td>
<td>Inactivating Enzyme</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>10</td>
<td>cmlA1</td>
<td>Efflux</td>
<td>Klebsiella, Staphylococcus</td>
</tr>
<tr>
<td>11</td>
<td>fexA</td>
<td>Efflux</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>12</td>
<td>cmlv</td>
<td>Efflux</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>13</td>
<td>cmr</td>
<td>Efflux</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>14</td>
<td>pexA</td>
<td>Efflux</td>
<td>Klebsiella, Shigella</td>
</tr>
</tbody>
</table>

### 2.2.1.13. Mechanism of resistance to Glycopeptides

Vancomycin resistance results due to production of altered D-ala-D-alamoieties involved as precursors in cell wall production. This modification results to reduction in a hydrogen bonding interaction probable between peptide and vancomycin (Pootoolal J, 2002). Modification of D-ala-D-alamoieties to D-ala-D-lac mediated by genes $VanA$, $VanB$ and $VanD$ decreases binding affinity of vancomycin by 1000 folds. Modification of D-ala-D-alamoieties to D-ala-D-ser mediated by genes $VanC$, $VanE$ and $VanG$ decreases binding affinity of vancomycin by 6 folds. $vanA$ and $van B$ are present on plasmids while $vanC1$,
vanC2/3, vanD, vanE, and vanG are exclusive to chromosome (Gao Y, 2002; Klare I, 1995; Depardieu F, 2007).

2.2.1.14. Mechanism of resistance to MLS antibiotics

Bacterial resistance mechanism to MLS group antibiotics (Macrolide-Lincosamide-Streptogramin B) include: modification of targets (ribosomal RNA) mediated by \textit{erm} genes, decrease in intracellular concentration through active efflux encoded by \textit{mef} genes and enzymatic drug inactivation which can be further subdivided in esterases, lyases, phosphorylases, and transferases mediate by \textit{ere} genes (Ungureanu V, 2010). Major mechanisms conferring broad spectrum resistance include action of rRNA methylases. rRNA methylases, methylate residues in 23S part of big 50S rRNA subunit and these methylated adenines restrict binding of drugs to respective 50S rRNA subunit binding sites (van Hoek AH, 2011). This led to cross resistance to all MLS class antibiotics attributed to the presence of overlapping binding sites in 23S region of 50S rRNA (Leclercq R, 2002).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{No.} & \textbf{Gene} & \textbf{Mechanism} & \textbf{Genera} \\
\hline
1 & \textit{cfr} & rRNA methylase & Staphylococcus \\
2 & \textit{ere(A)} & Esterase & Klebsiella \\
3 & \textit{ere(B)} & Esterase & Staphylococcus, Klebsiella \\
4 & \textit{ere(C)} & Esterase & Klebsiella \\
5 & \textit{erm(A)} & rRNA methylase & Staphylococcus, Streptococcus \\
6 & \textit{erm(B)} & rRNA methylase & Klebsiella, Staphylococcus, Streptococcus \\
7 & \textit{erm(C)} & rRNA methylase & Staphylococcus, Streptococcus \\
8 & \textit{erm(E)} & rRNA methylase & Shigella \\
9 & \textit{erm(F)} & rRNA methylase & Staphylococcus, Streptococcus, Shigella \\
10 & \textit{erm(G)} & rRNA methylase & Staphylococcus \\
11 & \textit{erm(Q)} & rRNA methylase & Staphylococcus, Streptococcus \\
12 & \textit{erm(T)} & rRNA methylase & Streptococcus \\
13 & \textit{erm(Y)} & rRNA methylase & Staphylococcus \\
\hline
\end{tabular}
\end{table}
<table>
<thead>
<tr>
<th>14</th>
<th><em>erm(33)</em></th>
<th>rRNA methylase</th>
<th>Staphylococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td><em>lnu(A)</em></td>
<td>Transferase</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>16</td>
<td><em>lnu(B)</em></td>
<td>Transferase</td>
<td>Staphylococcus, Streptococcus</td>
</tr>
<tr>
<td>17</td>
<td><em>lnu(C)</em></td>
<td>Transferase</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>18</td>
<td><em>lnu(D)</em></td>
<td>Transferase</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>19</td>
<td><em>lsa(B)</em></td>
<td>Efflux</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>20</td>
<td><em>lsa(C)</em></td>
<td>Efflux</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>21</td>
<td><em>mdf(A)</em></td>
<td>other</td>
<td>Shigella</td>
</tr>
<tr>
<td>22</td>
<td><em>mef(A)</em></td>
<td>Efflux</td>
<td>Klebsiella, Staphylococcus, Streptococcus</td>
</tr>
<tr>
<td>23</td>
<td><em>mef(E)</em></td>
<td>Efflux</td>
<td>Staphylococcus, Streptococcus</td>
</tr>
<tr>
<td>24</td>
<td><em>mef(G)</em></td>
<td>Efflux</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>25</td>
<td><em>mph(A)</em></td>
<td>Phosphorylase</td>
<td>Klebsiella, Shigella</td>
</tr>
<tr>
<td>26</td>
<td><em>mph(C)</em></td>
<td>Phosphorylase</td>
<td>Staphylococcus</td>
</tr>
<tr>
<td>27</td>
<td><em>mph(D)</em></td>
<td>Phosphorylase</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>28</td>
<td><em>mre(A)</em></td>
<td>Efflux</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>29</td>
<td><em>msr(A)</em></td>
<td>Efflux</td>
<td>Staphylococcus, Streptococcus</td>
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2.2.1.15. Mechanism of resistance to Mupirocin

Isolates demonstrating high level of mupirocin resistance shows presence of plasmid encoded *mupA* which encodes a novel isoleucyl RNA synthetase. Isolates with low-level mupirocin resistance usually have acquired base changes in the native isoleucyl RNA synthetase gene mediated by gene, *ileS* whose clinical significance is unclear (Udo EE, 2001; Hodgson JE, 1994; Antonio M, 2002, Patel JB, 2009). In contrast a few cases
involves presence of mupA gene conferring low level of resistance but indicating their presence on chromosome rather than on plasmid (Ramsey MA, 1996). It has been observed for triclosan, tetracycline, and trimethoprim that mupA gene may co-transfer with other antimicrobial resistance genes (Cookson BD, 1998).

2.2.1.16. Mechanism of resistance to Oxazolidinones

Oxazolidinones, the new synthetic drugs with decent penetration and accumulation capacity in bacterial pathogens are 

cidal for wide spectrum pathogens including Gram-positive bacteria, including methicillin- and vancomycin-resistant staphylococci, vancomycin-resistant enterococci, penicillin-resistant pneumococci and anaerobes. Clinical resistance against gram negative bacteria is due to presence of efflux pumps (Anderson RJ, 2012). Oxazolidinone resistance is rarely discovered and is chiefly attributed to alterations in 23S rRNA site (Bozdogan B, 2004). It is only the antibiotics that has made its way to therapeutic use since 1960’s (Walsh and Wright 2005).

2.2.1.17. Mechanism of resistance to Lipopeptide antibiotics

Lipopeptide antibiotic, daptomycin with its novel mechanism of dissipating membrane potential presently faces emerging heterogeneous resistance (Jared A, 2001), possibly due to loss of membrane protein chaperone to which it interacts. An important factor in development of stable and clinically significant resistance is heterogeneity of daptomycin MICs for susceptible strains (Kaatz GW, 2006).

2.2.1.18. Mechanism of resistance to Polymyxins

Polymyxin resistance to gram-negative bacteria initializes with electrostatic interaction between the positively charged peptide and the negatively charged LPS. PmrA/PmrB and PhoP/PhoQ two-component regulatory systems leads to Lipopolysaccharide modification which further restricts or reduces this initial interaction conferring resistance to polymyxins (Zavascki AP, 2007). Such a resistance has been witnessed less than 10% while its occurrence is higher in Mediterranean basin region and others like Korea and Singapore (Falagas ME, 2010).
2.2.2. Need-of-Hour

Bacterial pathogens that cause fatal infections are likely to be resistant to at least one of the drugs commonly used in treatment of bacterial infections. 
- Infectious Disease Society of America (IDSA) in 2004

As seen, bacterial pathogens employ novel and unfathomed resistance mechanisms which are out of reach of antibiotics. Antibiotic resistance is now a global health problem which finds its roots in extensive prescribing of antibiotic drugs and their improper use in medical treatments (Wester et al., 2002). Infection treatments are becoming very complicated and trivial due to emergence of highly multidrug resistant strains like methicillin-resistant Staphylococcus aureus (MRSA) and penicillin-resistant Streptococcus pneumonia (Reynolds et al., 2004; Karchmer, 2004). Lack of novel antibiotics is another major concern for society. Need-of-hour is novel class of antibacterial agents that could replace antibiotics or can be combined with antibiotics to combat killer pathogens (M. Hassan, 2012).

2.3. Bacteriocins

“Bacteriocins are ribosomally synthesized antimicrobial peptides produced by one bacterium that are active against other bacteria” (Mary C. Rea, 2011). Bacteriocins have notable differences from eukaryotic antimicrobial peptides with high potency and at low concentrations of pico- to nano-molar. Like AMPs form first line of defense of eukaryotic systems, bacteriocins provide competitive advantage to bacteria in competitive ecological niches for survival in turn killing other bacteria of environment. Bacteriocins have a very narrow spectrum of targets which includes mainly the species/ genera closer to its producer (Nissen-Meyer and Nes, 1997). Genetic determinants for production of bacteriocins are located on mobile genetic elements facilitating the transmission of traits in the community (Jack et al., 1995). It is estimated that 30-99% of bacteria and archaea, probably produce at least one bacteriocin (Sylvie Rebuffat, 2011).

Bioinformatics sources of bacteriocins include BACTIBASE and publicly available online BAGEL2 tool (Hammami R, 2007; de Jong A, 2006).
2.3.1. Classification

Credited to their heterogeneity bacteriocins are classified according to their mechanism of killing, common resistance mechanism, producing strains, biochemical and genetic characteristics (José Luis Parada, 2007).

**Klaenhammer Classification**

Klaenhammer classified bacteriocins into three groups Class I lantibiotics, Class II non-lantibiotics and Class III (Klaenhammer, 1993).

**Class I – Lantibiotics.** Small, heat stable and with high post translational modifications, lantibiotics are bacteriocins weighing less than 5 kDa ranging from more than 19 amino acids to about 50 amino acids. Bacteriocin nisin and its analogue subtilin belong to the class of lantibiotics (Sahl and Bierbaum, 1998).

Class I is further divided into Class Ia and Class Ib. Bacteriocin’s nisin, subtilin, lacticin 3147 and thuricin CD belongs to subclass Ia of lantibiotics which are comparatively elongated, flexible and positively charged peptides. Their mode of action includes formation of pores in in cytoplasmic membranes of target species. While subclass Ib are globular, less flexible, may carry negative or no charge for instance mersacidin bacteriocin. Their mode of action includes interfering with important bacterial enzymatic reactions. Structure of lantibiotic plantaricinC contains elements of both Class Ia and Class Ib again disputing the classification scheme (Turner DL, 1999).

Class I peptides in general are classified by presence of unusual amino acids like lanthionine, methyl-lanthionine, dehydrobutyrine and dehydroalanine (Deegan et al., 2006; Cotter et al., 2005a; Bierbaum and Sahl, 2009; Altena et al., 2000). Another classification suggests 11 subclasses for bacteriocins (M. Hassan, 2012).

**Class II - Non Lantibiotics:** These are small (25–60 amino acids), heat labile and non-modified except the formation of disulphide bridges (M. Hassan, 2012; Jennifer
Cleveland, 2001). Conventionally these are divided into 4 subclasses: class IIa, class IIb, class IIc and class IIId while some others mention only three classes excluding class IIId.

Class IIa peptides contain an N-terminal consensus sequence (Tyr–Gly–Asn–Gly–Val) and are known for their firm antilisterial activity. Example: pediocin PA-1 and sakacin P (Venema et al., 1997; M. Hassan, 2012).

Class IIb peptides include bacteriocins having 2 peptides depending upon complementary action of both the peptides to form active poration complex. Sequences of both the peptides are different yet both are usually encoded by adjacent genes. Example: ABP-118, lactococcin G and plantaricin EF and JK (Jennifer Cleveland, 2001).

Class IIc – These includes cyclic bacteriocins with ring structures. Both class IIb and class IIc can use sec secretion system for secretion so consequently class IIc was suggested to be merged with IIb (Clintas et al., 1997; Nes et al., 1996).

Class IIId includes large single peptides with an ability to form large complexes with other macromolecules and are sensitive to heat (Klaenhammer, 1993).

Class III - These are heat labile large peptides and are further divided into subclass IIIa or bacteriolysins and subclass IIIb (Bastos M.C.F., 2010). For example: For example: Helveticins J and V-1829, acidophilucin A, lactacins A and B.

Class IV – these classes of bacteriocins are just experimentally characterized and include complex bacteriocins containing lipid or carbohydrate moieties (Oman T. J., 2011; Stepper J., 2011).
Figure 2.4: Proposed “Universal” bacteriocin classification scheme

Because of their great biochemical diversity, classification of bacteriocins is still under debate and different classifications have been suggested over the years. A universal classification scheme presented by Cotter et al. is given in figure 2.4 (Cotter PD et al., 2006). Classification of bacteriocins is still debated (Cotter PD, 2005).

2.3.2. Mode of Action of Bacteriocins
Mechanisms of action to combat the target cells suggested for bacteriocins include,

1. Alteration of enzymatic activity
2. Inhibition of spore germinations
3. Inactivation of anionic carriers via formation of pores (Abee, 1995; Martinez and De Matins, 2006)
4. Inhibition of cell wall synthesis (Wiedemann et al. 2001)
5. inhibits DNA gyrase
6. inhibits RNA polymerase
7. inhibits aspartyl-tRNA synthetase (Paul D. Cotter, 2013)

Lactic acid bacteria are not capable enough to kill gram negative bacteria because of presence of the outer membrane that hinders the site of bacteriocin action, cell membrane (Morisset et al., 2004). Inhibition of cell wall synthesis and pore formation are the two the mechanisms utilized by LAB bacteriocins to exert antimicrobial effect in which it employs pore formation generally (Wiedemann et al., 2001).

González-Martínez et al. (2000) suggests that both class I and class II bacteriocins employ same mode of action to combat target cells. Initial interaction between the target cell and peptide bacteriocin involves electrostatic force due to opposite charges yet taking into account its property of specificity; it is supposed that bacteriocin binds to receptors on selective cells. To sustain this supposition many such specific receptors have been reported (M. Hassan, 2012). Class I bacteriocins use lipid II molecule as a docking molecule on target cells. Function of lipid II remains common in many bacteria’s and hence these lantibiotics have a broad spectrum of action encompassing varied genera of gram positive organisms (Brotz et al., 1998b). Peptides bind to the plasma membrane via electrostatic interactions with anionic phospholipids and thereby getting into membrane with a reorientation which depends on the membrane potential. The monomers of bacteriocin form proteolytic aggregates which outcomes into formation of pores (Bruno and Montville, 1993). Pore formation results into outflow of low molecular weight compounds like K⁺, H⁺, phosphate, mg²⁺ among other leading to dissipation of the proton motive force (Eijsink et al., 2002). Proton motive force which has a role in ATP synthesis, in active transport and in movement of bacteria decreases due to pore formation and in turn the synthesis of macromolecules and production of energy are inhibited which results into cell death (Bruno and Montville, 1993).

Other class I peptides, such as the thiopeptides and bottromycins, control Gram-positive bacteria by targeting translation (Paul D. Cotter, 2013).
Lantibiotic, nisin shows dual mode of action. They can bind to lipid II, the main transporter of peptidoglycan subunits from the cytoplasm to the cell wall, and therefore prevent correct cell wall synthesis, leading to cell death (Paul D. Cotter, 2005; Hasper et al., 2006). Another mode of action involves binding of lipid II to the lantibiotics ring structure of nisin which leads to formation of deadly pores containing nisin and lipid II as shown in figure 2.5 (Hsu et al., 2004). Many lantibiotics with ring structure at their N-
terminal follow the same mode of action which involves formation of lipid II-nisin complex.

![Figure 2.6: Mode of action of Nisin](image)

General mode of action of class II bacteriocins depends upon the amphipathic helical structure allowing them to insert into the membrane of the target cell and hence ground cell termination (Paul D. Cotter, 2005). Class IIa bacteriocins like pediocin PA-1, enterocin P, enterocin A and sakacin P which are potential against Listeria and Enterococcus species and class IIb bacteriocins like lactococcin A and lactococcin B recognize mannose-phosphotransferase system (Man-PTS) on the bacterial target cells (M. Hassan, 2012). PTS transport systems are exclusive only to bacterial phyla while are absent in eukaryotes making them a very attractive drug target (Saier and Paulsen, 1999). As shown in figure man-PTS system has four subunits IIABCD from which IIC and IID form a trans-membrane-located complex, while IIA and IIB are revers-ibly associated with their IIC and IID from the cytoplasmic side (Postmaet al., 1993). Membrane located proteins IIc and IID become docking targets for class IIa bacteriocins whose binding with them results into conformational changes in man-PTS rendering the transport system irreversibly open. This causes leakage of cellular solutes and eventually cell death (M. Hassan, 2012).
Class IIb bacteriocins which have two peptides and their action mechanism depends upon complementation of two peptides. For instance, Lactocin 705 is a bacteriocin with two peptides lac705α and lac705β (33 amino acids each). As a complex of both these peptides lactocin 705 exerts its interaction through attachment with cell wall associated binding sites on target cells. A game of charges is involved in the mechanism of action in which net positive charge of 14C terminal amino acids of bacteriocin would neutralize negative charge of techoic acids and lipotechoic acids of cell wall. lac705β further forms pores which inclines permeabilization and hence the cell death. The mechanism is still under supposition (José Luis Parada, 2007).

Class III includes high molecular weight bacteriocins called as bacteriolysins such as lysostaphin, can function directly on the cell wall of Gram-positive targets, leading to death and lysis of the target cell (Paul D. Cotter, 2005).

Bacteriocins that have the capacity to inhibit gram negative bacteria control their target bacteria by interfering with DNA, RNA and protein metabolism while some bacteriocins like MccE492 exert antibacterial action through formation of pores.

- Microcin B17 (MccB17) inhibits DNA gyrase
- MccJ25 inhibits RNA polymerase
- MccC7-C51 inhibits aspartyl-tRNA synthetase
2.3.3. Bacteriocins of Gram positive bacteria

Gram positive bacteria harbors small and heat stable Bacteriocins which are directed against a broader spectrum of bacteria compared to the spectrum of gram negative bacteria (Ingolf F. Nes, 2007).

2.3.3.1. Staphylococcus species

*Albococcus epidermidis* (*Streptococcus epidermidis*) encodes lantibiotic epidermin on plasmid by gene*epiA*, lantibiotic Pep5 encoded by *pepA*, lantibiotic epilancin 15X, lantibiotic epilancin encoded by *elkA* which are lanthione containing bacteriocins active on gram positive bacteria. The bactericidal activity of lantibiotics is based on depolarization of energized bacterial cytoplasmic membranes, initiated by the formation of aqueous transmembrane pores (Van de Kamp M, 1995; Ekkelenkamp MB, 2005; Meyer C, 1995; Blaesse M, 2000). Lantibiotic streptococcin A-M49 encoded by *scnaA*, lantibiotic streptococcin A-FF22, lantibiotic streptin are lantibiotic bacteriocins that have the same mode of action as bacteriocins from *Staphylococcus epidermidis* (Hynes WL, 1994). Aureocins A70, A53, and 215FN from *S. aureus* and Pep5, epidermin, epilancin K7 and epicidin 280 from *S. epidermidis* are tested for activity against 165 strains of S.
aureus and 74 strains of S. agalactiae. Activity against most of strains was demonstrated by aureocin A53 and epidermidin. A combination of aureocins A53 and A70 broadened the antibacterial spectrum (Varella Coelho ML, 2007).

2.3.3.2. Streptococcus species

In streptococci, lantibiotics are predominant bacteriocins mostly belonging to elongated cationic type A lantibiotics. Two-peptide lantibiotics have also been isolated from streptococci. Lantibiotic salivaricin A strongly inhibits S. pyogenes and was first found in S. salivarius (Ross KF, 1993; Ingolf F. Nes, 2007). Salvaricin A1 to A5 are the structural variants of salivaricin A to be discovered in streptococcus species. All these six variants are similar in inhibition spectrum due to minor difference of 1-2 amino acids in primary sequence. SalA1 type bacteriocins are produced by broad range of species including S. pyogenes, Streptococcus dysgalactiae, and Streptococcus agalactica (Wescombe PA, 2006). Streptolycin S, a bacteriocins-like toxin is produced by group A streptococcus yet it does not antagonize bacteria (Fuller JD, 2002; Humar D, 2002; Nizet V, 2000). It is suggested that two genes present in blp operon of pneumococci, blpM and blpN comprise a type IIb, or two-component, bacteriocins. Deletion of entire blp operon leads to loss of immunity suggesting presence of blpMN genes on this operon (Eijsink VG, 2002; Nissen-Meyer J, 1992).

2.3.4. Bacteriocin of gram negative bacteria

The first bacteriocin to be described was identified in 1925 from E. coli, gram-negative bacteria. From gram negative bacteria, enterobacteriaceae is main source for bacteriocins mainly divided into 2 major families. One family includes high molecular mas proteins called as colicins and low molecular weight proteins called as microcins (Sylvie Rebuffat, 2011).

2.3.4.1. Klebsiella species

Klebsiella pneumoniae encodes channel forming bacteriocin, Microcin E492 from gene mceA. Microcin is capable of forming cation-selective channels and is active on enterobacteria showing high activity against E. coli while being inactive on gram-
negative species and fungi. When Microcin protein is unmodified, it demonstrates activity against \textit{E.coli} and \textit{S.enteritidis} while on modification when siderophore ester is present at Ser-99 then its activity is extended, encompassing \textit{E.cloacae} and \textit{K.pneumoniae} species also (Thomas X, 2004).

\subsection*{2.3.4.2. Shigella species}

Colicin-E1 encoded by \textit{cea} gene on plasmid pKY-1 is a channel-forming colicin in shigella species. This class of transmembrane toxins depolarizes the cytoplasmic membrane, leading to dissipation of cellular energy which is deleterious for cells. Colicins are polypeptide toxins produced by and active against \textit{E.coli} and closely related bacteria (Higashi M, 1986). Molecular weight of colicins generally ranges from 30-80 kDa and the production of colicins is mediated by the SOS response regulon, playing a role in the response of many bacteria to DNA damages (Sylvie Rebuffat, 2011).

\begin{table}[h]
\centering
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\textbf{No} & \textbf{Protein Name} & \textbf{Source} & \textbf{GI} & \textbf{PMID} & \textbf{Target Genera} \\
\hline
\hline
2 & antibacterial protein (phenol soluble modulin ) & \textit{Staphylococcus aureus} subsp. aureus COL & 57284471 & Predicted & Antimicrobial  \\
\hline
3 & antibacterial protein (phenol soluble modulin ) & \textit{Staphylococcus aureus} subsp. aureus COL & 57284472 & Predicted &  \\
\hline
4 & USA300_FPR 3757 antibacterial protein & \textit{Staphylococcus aureus} subsp. aureus & 87126339 & Predicted &  \\
\hline
5 & carnocyclin A & \textit{Carnobacterium maltaromaticum} & 186898221 & 18552180 & \textit{S. aureus} ATCC 25923, \textit{S. aureus} ATCC 6538, \textit{S. aureus} ATCC 29213  \\
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\caption{List of bacteriocins from gram positive and negative bacteria}
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<td>37</td>
<td>Microcin L</td>
<td><em>Escherichia coli</em></td>
<td>30026596</td>
<td><em>Shigella sonnei CIP5236, Shigella flexneri CIP5236</em></td>
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<td>Microcin J25</td>
<td><em>Escherichia coli</em></td>
<td>48429009</td>
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<td>Lantibiotic epidermin</td>
<td><em>S. epidermidis</em></td>
<td>11101502</td>
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<td><em>S. epidermidis</em></td>
<td>7556197</td>
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<td>Lantibiotic epilancin 15X</td>
<td><em>S. epidermidis</em></td>
<td>15792796</td>
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<td><em>S. epidermidis</em></td>
<td>7607233</td>
<td><em>Shigella sonnei, Klebsiella species</em></td>
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<td><em>Gram-positive bacteria</em></td>
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<td><em>Klebsiella pneumoniae</em></td>
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<td>Enterobacteria, <em>E. coli</em>, <em>S. enteritidis</em>, <em>E. cloaca</em>, <em>K. pneumoniae</em></td>
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<td>Protects the cell against microcin</td>
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