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Emerging resistance of antibiotics among various bacterial infections

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Abstract

Antibiotics are substances that have a wide range of uses for treating bacterial illnesses. They may be synthetic, naturally occurring, or semi-artificial. The use of antibiotics has enabled the treatment of bacterial infections, saving and enhancing the health of numerous patients around the globe. Antibiotics, however, are not working well enough to stop the spread of infection and the associated mortality rates. However, antibiotic resistance among common community-acquired infections has been on the rise, as has the number of medications to which they are resistant. Data from several researches provide significant evidence that antibiotic use and resistance are interrelated. The highest levels of resistance are found in nations with the highest per capita antibiotic use. Consumption of antimicrobial agents and the prevalence of antibiotic resistance are intricately related. The main causes of resistance are selective antibiotic pressure, the spread of resistant bacteria, and the transfer of resistance genes across bacteria. However, the impact of selective pressure varies depending on the type of bacteria and antibiotic class. The community should refrain from using a lot of antibacterials, especially broad-spectrum antibiotics. When possible, narrow-spectrum penicillins should be employed. Long-term prospective studies that track patterns of antibiotic usage and resistance are required. National measures intended to lessen the resistance of microorganisms to antibiotics should be based on reliable data on antimicrobial consumption and resistance.

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Introduction

Before the beginning of 20th century, high mortality as well as morbidity was associated with the infectious diseases. Men and women had an average life of 47 years with men living for 46 years whereas women lived 48 years of age, even during the industrial period. Infectious diseases like pneumonia, syphilis, smallpox, typhus, diphtheria, cholera, plaque, typhoid fever, and tuberculosis were uncontrolled (Shrestha, 2005).

Sir Alexander Fleming (1881-1955) in 1928 accidently discovered penicillin which brought upon the revolution in the antibiotics (Fleming, 1929). The credit of purifying the penicillin G for the first time goes to Howard Florey and Ernst Chain in 1942, but its wide availability to the military happened for the first time in 1945. This event is markedly the start of an era of antibiotics. In this era many new antibiotics were discovered, and time frame from the 1950s to the 1970s is referred to as golden era of novel antibiotics discovery, and from that period of time there have been no new discoveries of the antibiotics. Following that period, new drug discovery relied on the modifications of the already existing antibiotics (Aminov, 2010).

When 20th century started, almost all of the patients suffering with the Hib or pneumococcal meningitis as well as majority of the meningococcal meningitis patients faced death owing to the disease (Swartz, 2004). Using particular antiserums in the 1906 delivered intrathecally for treating meningococcal meningitis resulted in reducing the mortality associated with the meningococcal meningitis to 30.9% whereas reduction to 85% in the mortality of Hib meningitis was reported (Flexner, 1913; Swartz, 2004). Introduction of the antibiotics like chloramphenicol, sulfonamides, and penicillin for the use of treating bacterial meningitis following 1920s proved to be major breakthrough. This caused Hib, meningococcal, and pneumococcal prognosis to show distinctive improvement (Swartz, 2004). Since then, researchers have conducted a lot of studies on the best way to treat bacterial meningitis, and new antibiotics have been developed. However, there is still more work to be done in order to improve the outcomes for people with this disease. Medical treatments against infectious diseases have changed a lot over the years. Clinicians now have vaccines as an option. Vaccines have been successful in completely or nearly eradicating viruses and bacteria. For example, smallpox has been eliminated whereas polio has also been nearly eradicated and the incidence of diseases like mumps, diphtheria, , pertussis, rubella, measles, and tetanus has decreased by more than 95% (Rappuoli *et al.*, 2011). Today, vaccines can be developed quickly and efficiently with the help of reverse vaccinology and other innovative methods. This scientific approach allows for antigens identification in a detailed and comprehensive way, resulting in high quality vaccines (Sette and Rappuoli, 2010).

Antibiotics

Antibiotics are compounds that can be used to treat bacterial infections in a variety of applications. They can be naturally occurring, synthetic or semi-synthetic (Davies and Davies, 2010). The use of antibiotics has led to the treatment of infections caused by bacteria, which has saved and improved the health of many patients all over the world. (Sette and Rappuoli, 2010). However, antibiotics are proving not enough for the control of the spread of infection and its consequent mortality rates. Antibiotics, antibacterials in particular, only work against bacteria. Furthermore, antibacterials are becoming less effective as bacteria mutate and become resistant to more and more drugs (Arias and Murray, 2009; Davies and Davies, 2010; Nikaido, 2009).

There are two types of antibacterials: bacteriostatic and bactericidal. Antibacterials that kill bacteria by making cell wall or membrane a target is referred to as bactericidal, while those which results in slowing or inhibition of bacterial growth are called bacteriostatic. Inhibiting protein synthesis or inhibition of some bacterial metabolic pathways is how bacteriostatic agents work. Due to the bacteriostatic action of such agents in the inhibition

of the pathogenic bacterial growth, some of the times it proves difficult to establish a boundary between bactericidal and bacteriostatic, particularly in the cases where there is higher concentrations of bacteriostatic agents being used, and in such cases they might act as a bactericidal agent (Aminov, 2010). There are two types of antimicrobial drugs, synthetic and natural. The synthetic drugs, like the sulfonamides and quinolones, are manufactured in a lab. The second type, antibiotics are produced by microorganisms. In past years, there has been development in more and more semi-synthetic drug. These drugs are chemical derivatives of the antibiotics, which makes the distinction between synthetic and natural antibiotics more blurry (Ullah and Ali, 2017). Cefamycins, cephalosporins, gentamicin, and benzylpenicillin are among the examples of the natural antibiotics or antibacterials that are well known. Although high toxicity is exhibited by natural antibiotics than the synthetic antibacterials, semi-synthetic antibiotics like amikacin and ampicillin have low toxicity and increased effectiveness. Synthetic antibiotics are designed to be even more effective and less toxic, making them a better choice than natural antibiotics such that there is no exposure of the bacteria to the compounds of the drugs until their release. Norfloxacin and moxifloxacin are two promising synthetic antibiotics (Oloke, 2000). Most antibiotics used in commercial settings are produced by fungi or bacteria as part of their defensive mechanisms. Penicillin, one of the most well-known antibiotics, is produced by mold Penicillium. However, many of the commonly used antibiotics like tetracycline and streptomycin originate from soil bacteria in genus *Streptomyces*(Procópio *et al.*, 2012). Antibiotics as secondary metabolites are produced by microbes under specific conditions. It is not fully understood what their natural function is, although it is believed owing to a common theory that antibiotics play a role in competitively inhibiting the growth of neighboring bacteria to eliminate or minimize the burden on the surrounding local resources (Cornforth and Foster, 2015). In other instances, transcriptional responses of cell have been found to be affected by the antibiotics where they could be acting as the signaling molecules thereby regulating responses as well as interactions inside the bacterial communities (Goh *et al., 2002;* Linares *et al., 2006)*. In the recent years, a suggestion has been made that antibiotics are a part of an organism's physiological function which produces them and play a role in regulating growth rate of the cell (Esnault *et al.*, 2017)(as in table 1).

Table 1. Important classes of antibiotics, their cellular binding site, and the mechanism for inhibition of bacterial growth.

Class	Examples	Binding site	Mechanism of action
Aminoglycosides	Gentamicin Kanamycin Streptomycin	Ribosome	Inhibit protein synthesis
Tetracyclines	Tetracycline	Ribosomes	Inhibit protein synthesis
Amphenicols	Chloramphenicol	Ribosome	Inhibit protein synthesis
Lipopeptides	Daptomycin	Membrane	Disrupt cell membranes
Ansamycins	Rifampicin	RNAP	Inhibit RNA synthesis
Macrolides	Erythromycin	Ribosome	Inhibit protein synthesis
Beta-lactams	Carbapenems Cephalosporins Penicillins	PBPs	Inhibit cell wall synthesis
Oxazolidinones	Linezolid	Ribosome	Inhibit protein synthesis
Glycopeptides	Vancomycin	Peptidoglycan	Inhibit cell wall synthesis
Sulfonamides	Sulfamethoxazole	DHPS	Inhibit folic acid synthesis
Lincosamides	Clindamycin	Ribosome	Inhibit protein synthesis
Quinolones	Ciprofloxacin Nalidixic acid	Topoisomerases	Inhibit DNA replication
Polymyxins	Colistin Polymyxin B	Membrane	Disrupt cell membranes
Others	Fosfomycin Fusidic acid Trimethoprim	MurA EF-G DHFR	Inhibit cell wall synthesis Inhibits protein synthesis Inhibit folic acid synthesis

Classification on the basis of activity spectrum is a different way of classifying antibacterial agents or the antibiotics,that is based on the target specification. Owing to this category, antibacterial agents are either broad spectrum or narrow spectrum.

The interpretation of these terminologies have not been done specifically from the time of their use in the history of the antibiotics, but in the recent times they have got a clear meaning both in industrial as well as academic fields (Acar, 1997; Carbon and Isturiz, 2002). Those antibacterials which acts on a narrow range of the microbes are considered as the narrow spectrum antibacterials, as their action is established against only the gram-positive bacteria or the gram-negative bacteria, whereas broad spectrum antibacterials works against a wide variety of gram negative and gram-positive pathogens. Generally, preference is given to the narrow spectrum antibacterials over the broad spectrum due to the least collateral damage caused to the normal microbiota as well as narrowing down the chances of a superinfection. Additionally, narrow spectrum antibacterials contribute in a lesser way to the development of the resistance as it is only dealing with a single microbe (as in table 2).

Table.2. List of broad- and narrow-spectrum antibacterial drugs.

Broad-spectrum antibacterials (examples)	Narrow spectrum antibacterials (examples)
Ampicillin along with its derivative called as amoxicillin are termed as antibacterials having a broad-spectrum. Amoxicillin/clavulanic acid is commonly called coamoxiclav, is the antibiotic used for the treatment of numerous infections caused by the bacteria	Benzathine penicillin G, clometocillin, penicillin V, propicillin, procaine penicillin, penamecillin, azidocillin, penicillin G, and pheneticillin are first generation antibacterials that are sensitive to ß-Lactamase and are accounted among the category of narrow spectrum antibiotics
Quinolones (King *et al*., 2000) like Levaquin (levofloxacin), Cinobac (cinoxacin), Zagam (sparfloxacin), Noroxin (norfloxacin), Maxaquin (lomefloxacin), NegGram (nalidixic acid), Trovan(trovafloxacin), Cipro (ciprofloxacin), Avelox (moxifloxacin), Floxin (ofloxacin), Factive(gemifloxacin), and Tequin (gatifloxacin) are accounted among the antibiotics having a broad spectrum	1st generation showing resistance towards the ß-Lactamase are temocillin, Cloxacillin (dicloxacillin flucloxacillin), nafcillin, oxacillin, and methicillin and are considered as the antibiotics that have a narrow spectrum
Dibekacin, netilmicin, neomycin E (paromornycin), kanamycin A, tobramycin, sisomicin, neomycins B, C, amikacin, and gentamicin are accounted as the Aminoglycosides class of drugs and being the antibiotics having a broad spectrum (Kotra *et al*., 2000)	Both 1st and 2nd generation cephalosporins demonstrate relatively a narrow spectrum activity
3rd, 4th, and 5th generation cephalosporins show relatively extended, ranging to broader activity spectrum	Rifampin, pyrazinamide, ethambutol, polymixins, isoniazid, vancomycin, glycopeptide, sulfonamides, nitroimidazoles, bacitracin, and clindamycin comprise this group of the antibiotics
Broader activity range is exhibited by the carbapenems such as imipenems (Zhanel *et al*., 2007)	
Roxithromycin, dirithromycin, azithromycin, erythromycin, and clarithromycin comprise the class macrolides and are accounted in the category of antibiotics with broad spectrum (Hof, 1994).	
Minocycline, meclocycline, lymecycline, oxytetracycline, tetracycline, tigecycline, chlortetracycline, demeclocycline, and methacycline are accounted in the category of the antibiotics that show a broad spectrum activity	
Chloramphenicol	
Ticarcillin is a carboxypenicillin which demonstrates a broad activity spectrum	
Rifamycins also demonstrate broad spectrum activity (Floss and Yu, 2005).	

Mechanism of action of different antibiotics for gram positive bacteria

The primary classes of the antibiotics mainly target the enzymes involved in the biosynthesis of the cell wall as well as the substrates (for example, vancomycin, bacitracin and beta-lactams), protein synthesis of the bacteria (for example, aminoglycosides, tetracyclines, chloramphenicol, mupirocin, fusidic acid, macrolides, linezolid, and clindamycin), repair as well as the replication of

nucleic acid inside the bacteria (for example, co-trimoxazole sulfamethoxazole that infers an anti-metabolite mechanism, quinolones and rifampicin), and cell membranes (for example, mupirocin).

The need of novel antibiotics for the treatment of diseases is growing especially for the infections that gram positive bacteria induce. Numerous pathogenic bacteria are developing resistance against the potent antibiotics that are being utilized for their treatment. The situation turns more alarming by the fact that the resistance is not limited to a single agent but might extend to several antibiotics. The newer antibiotics with their direct spectrum are able to bypass the resistance mechanisms due to the novelty of their action mechanisms (Critchley *et al.*, 2003). So, a new regimen has been provided by such antibiotics in terms of chemotherapy against microbes and serve as a priceless tool against the rising issue of antibiotic resistance. The newer antibiotics used against gram-positive bacteria are oxazolidinones (linezolid), daptomycin, Cationic antimicrobial peptides, ketolides, tigecycline, oritavancin and dalbavancin, mechanism for which will be discussed in the subsequent section along with the conventional antibiotics.

Cell wall active agents

β-Lactams mechanism of action

Beta-lactams kill all the susceptible bacteria via inhibiting their cell wall synthesis in gram-negative as well as gram positive bacteria both and are regarded as bactericidal agents. There are three main classes of β-lactams namely, carbapenems, cephalosporin, and penems which are considered to be potential drugs for treating serious conditions caused by gram positive bacteria.

Peptidoglycan is the primary constituent that makes up the cell wall of the bacteria. It is heteropolymer and is composed up of the strands of glycan where there are N-acetylmuramic acid residues and β-1,4-linked N- acetylglucosamine which exist in an alternating manner. Carboxyl group of every residue of N-acetylmuramic acid is substituted by the subunit of pentapeptide that has an alternating l- and d-amino acids and a dibasic amino acid, that is usually meso-diaminopimelic acid (m-DAP) in majority of the gram-negative bacteria as well as some of the gram-positive bacteria, for instance some Bacillus species or l-lysine in majority of the gram-positive bacteria. Cross linking of the peptide subunit of one of the chains with a neighbor chain give rise to the three dimensional structure of the peptidoglycan network (Vollmer and Bertsche, 2008). Contrary to the uniformity of the glycan structure, the moiety of the peptide exhibits notable variations among the organisms. The commonest pentapeptide found is l-Ala$_{(1)}$-d-Glu$_{(2)}$-(m-DAP or l-Lys)$_{(3)}$-d-Ala$_{(4)}$-d-Ala$_{(5)}$. Formation of the cross linking of the peptides is achieved by an enzymatic action which links d-Ala$_{(4)}$ from one of the peptide chains to the other chain m-DAP or l-Lys$_{(3)}$ free amino group. Peptidoglycan cross linking is either achieved directly or by short peptide bridge as noted in many of the gram-positive bacteria. Such as cross linking in the *S. aureus* is done by five glycines (van Heijenoort and Gutmann, 2000). The last stage of the synthesis of peptidoglycan takes place outside of the cells when glycan strand polymerization is catalyzed by the PBPs (transglycosylation) and cross linking between the glycan chains occur (transpeptidation). PBPs are usually classified into: High-molecular-mass (HMM) PBPs. Classification of the HMM PBPs can be done further into either class A or B due to the functional domains they possess. PBPs belonging to class A are bifunctional meaning they have both the transpeptidase as well as transglycosylase activities, whereas PBPs belonging to class B only have transpeptidase activity. HMM PBPs are important for the survival of the cells and are actually targeted by the β-lactams.Low-molecular-mass (LMM) PBPs. are often the peptidases that are not essential for the survival of the bacteria, and so are termed as minor targets targeted by the β-lactams (Sauvage and Terrak, 2016).

β-lactams have the ability to interact with the PBPs due to stereochemical similarity of the structure of

the β-lactams with residues of d-alanine-d-alanine which play their role in the peptidoglycan synthesis. Due to this blocking of transpeptidation reaction results in the form of bacterial cell wall integrity getting compromised subsequently leading to the lysis of the cell, followed by death. Modification in the structure of the PBPs due to mosaic structure formation following heterologous genes recombination or mutation causes lower affinities of the PBPs for the β-lactams and might be a potential explanation behind the affinities for beta-lactams and explains the acquired resistance process against the antibiotics, particularly for the gram positive bacteria (Zapun *et al*., 2008).

Mechanism of action of cephalosporins

Similar to all the β-lactams, the mechanism cephalosporin is through inhibiting the growth of a bacterial cell by the formation of a long term covalent acyl enzyme that target PBPs, the enzymes involved in the synthesis of the periplasmic cell wall and are attached to cytoplasmic membrane (Ryan *et al*., 2000; Hebeisen *et al*., 2001;Yoshizawa *et al*., 2002;Malouin *et al*., 2003;). Due to the significance of incorporating the MRSA in microbial spectrum, the study of such agents has been done specifically with respect to them binding with the PBP2a, which in an essential PBP playing role in the development of resistance in MRSA as it has lower affinity for majority of the conventional β-lactams.

Glycopeptides mechanism of action

Glycopeptide antibiotics such as vancomycin as well as teicoplanin are significant agents for treating Gram-positive pathogens that are resistant to multiple drugs, specifically MRSA. With nearly 20% of the enterococci found in the USA being resistant to the vancomycin and probability of the glycopeptide-resistance on a global scale by the MRSA (Malabarba and Ciabatti, 2001;Linden, 2002), oritavancin for treating VRE and the dalbavancin for targeting MRSA are developed.

Both teicoplanin as well as vancomycin binds with the pentapeptide-glycosyl cell wall intermediate, D-alanyl-Dalanine (D-Ala-D-Ala) terminal, thus preventing the transpeptidase reaction involved in the biosynthesis of the cell wall of the bacteria. Affinity against D-Ala-D-Ala is retained by both oritavancin as well as dalbavancin but might show further activity against an enzyme performing transglycosylase function in the biosynthesis of the peptidoglycan via the derivatized residues of the carbohydrate (Ge *et al.,* 1999; Malabarba and Ciabatti, 2001).

Moreover, the remarkable capability of the oritavancin and dalbavancin for the dimer formation and insertion into the membranes of the bacteria might results in improvement in the binding affinity as well as interaction with the residues of D-Ala-D-Ala of the precursors of nascent peptidoglycan (Beauregard *et al*., 1995; Malabarba and Ciabatti, 2001).

Topoisomerase inhibitors

Different classes of the compounds like synthetic quinolones, naturally occurring products like cyclothialidines and coumarins, different toxins secreted by the bacteria including B17 and CcdB as well as GyrI which is a regulatory factor, results in inhibition of both or one of the essential Type II DNA topoisomerase enzymes known as topoisomerase IV and DNA gyrase. Among such agents, there are only quinolones which play a significant role for clinically managing serious infections caused by the gram-positive bacteria (Abbanat *et al*., 2003).

Mechanism of action of quinolones

Activity of two of the enzymes that are closely related with one another, one of them being DNA gyrase which consists of GyrB and GyrA subunits and other one being multi subunit topoisomerase IV which play a role in controlling the topology of the bacterial DNA as well as the chromosome function. Apparently quinolones form stable ternary complexes with DNA and enzyme that causes inhibition of the synthesis of DNA due to the replication fork blocking (Drlica and Zhao, 1997). Generally, in *S. aureus*, quinolones target topoisomerase IV whereas in *Escherichia coli*, they target DNA gyrase, but there also have been

reports of exceptions (Discotto *et al.*, 2001; Roychoudhury *et al.*, 2001; Hooper, 2003).

While in the *S. pneumoniae*, there exists some complexities. In vitro, gemifloxacin has reportedly demonstrated better inhibition of the topoisomerase IV compared to DNA gyrase (Heaton *et al.*, 2000; Morrissey and George, 2000; Yague *et al.*, 2002), However it has been suggested by the stepwise mutant selection experiments that in vitro, this drug targets both of the enzymes, with slight incline towards the DNA gyrase (Heaton *et al.*, 2000). Inhibition of topoisomerase IV has also been reported by garenoxacin in *S. pneumoniae* at low concentrations compared to DNA gyrase (Yamada *et al.*, 2000). Nonetheless, rise of the pneumococci first step mutants in the GyrA, indicate that the main target inside bacterial cell is DNA gyrase (Hartman-Neumann *et al.*, 2001). Contrary to that, it has been reported that sitafloxacin inhibits the topoisomerase IV as well as DNA gyrase in the *S. pneumoniae*, where the affinity is comparable (Morrissey and George, 1999; Onodera *et al.*, 1999). Newer quinolones share a characteristic feature with no regards to what their primary target is for the *S. pneumoniae*, which is the better affinity for topoisomerase and DNA gyrase both. Due to this, such compounds in general inhibit strains of *S. pneumoniae* from growing at the lower concentrations compared to the old quinolones like ciprofloxacin.

Protein synthesis inhibitors

Ketolides mechanism of action

Ketolides are described as semisynthetic derivatives of erythromycin, which was the first macrolide. Macrolides have a activity spectrum mainly against the gram positive bacteria and are conventionally used as beta-lactams alternative to treat infections of skin as well as respiratory tracts and otitis media, It has been used historically against *Staphylococcus spp.,* and *Streptococcus* along with some of the gram negative bacteria like *Helicobacter pylori, H. influenzae* and atypical intracellular *Chlamydia spp.Mycoplasma* and *Legionella* (Blondeau *et al.*, 2002).

Resistance of the pathogens belonging to the gram-positive group to the macrolides like the newly discovered semisynthetic derivatives like clarithromycin and azithromycin has shown a worldwide increase. Ketolides like telithromycin and cethromycin retain their activity against many of the gram-positive pathogens which are otherwise resistant to the macrolides. Target of both the macrolides as well as ketolides is the prokaryotic ribosome 50S subunit and bind to the 23S rRNA domain V reversibly (Hansen *et al.*, 1999; Xiong *et al.*, 1999;Schlünzen *et al.*, 2001). Protein synthesis inhibition is resulted due to nascent peptides being released prematurely from the complex of mRNA and ribosome (Garza-Ramos *et al.*, 2001; Menninger, 1995) and probably by interfering with ribosomal proteins assembly on 23S rRNA (Champney and Tober, 1998; Champney, 1999;Douthwaite and Champney, 2001).

Mutational analyses and RNA foot printing experiments along with the crystallographic studies indicate that there is a direct interaction between the residues of domain V of 23S rRNA (A2059, G2505 and A2058) and the ketolides as well as macrolides (Douthwaite and Aagaard, 1993; Hansen *et al.*, 1999; Schlünzen *et al.*, 2001; Xiong *et al.*, 1999). Ketolides bind additionally to the domain V A2609 bases (Champney and Tober, 1998) as well as A752 of domain II (Hansen *et al.*, 1999; Xiong *et al.*, 1999; Douthwaite *et al.*, 2000), and result in increasing the affinity of the ribosomal binding and probably posing as an explanation of the increase in the potency against the gram positive cocci which are resistant and susceptible to the macrolides (Douthwaite, 2001; Douthwaite and Champney, 2001; Douthwaite *et al.*, 2000).

Mechanism of action of Oxazolidinones (linezolid)

Linezolid is synthetic oxazolidinone agent that is antimicrobial, binds to ribosomes inhibiting protein synthesis inside the microbe (Aoki *et al.*, 2002; Champney and Miller, 2002). This antibiotic acts reversibly and by blocking the protein synthesis initiation complex formation by binding to the 23S

rRNA subunit closer to interface which forms with 30S ribosomal subunit (Hutchinson, 2003).

Binding of the linezolid takes place closer to sites of binding for lincomycin and chloramphenicol as there is competition of linezolid with these two agents (Lin *et al.*, 1997; Swaney *et al.*, 1998). Nonetheless, there is a difference between these antimicrobials in term of their mechanism of action, with inhibition of formation of peptide bond by chloramphenicol and inhibition of the formation of initiation complex by linezolid.

This mechanistic difference results in infrequent cross resistance among lincomycin or chloramphenicol and linezolid. As linezolid mechanism of action is novel, it demonstrates similar activity against bacteria that are either susceptible or resistant against antibiotics in vitro as well as show activity against pathogenic microbes that show resistance against vancomycin and methicillin (Saravolatz and Eliopoulos, 2003). Studies conducted in vitro proved linezolid to have good activity against majority of the gram-positive pathogens that are medically important (Rybak *et al.*, 2000).

Mode of action of Glycylcyclines: tigecycline

Glycylcyclines are a modified form of tetracyclines which were selected so that the two main resistance mechanisms i.e., efflux and ribosomal protection against the tetracycline can be avoided. Tigecycline (9-[t-butylglycylamido]-minocycline) is broad-spectrum derivative of glycylcycline, which shows structural relations with tetracyclines, and shows efficacy against the gram-positive bacteria that has high resistance (Abbanat *et al.*, 2003), such as penicillin-resistant *S. pneumoniae* and MRSA.Tigecycline inhibits protein synthesis by binding with 30S ribosomal subunit.

It is thought that it blocks the amino-acyl tRNAs to enter ribosomal A site, thus resulting in the prevention of peptide elongation (Projan, 2000). The mechanism used is deemed as bacteriostatic (Projan, 2000).

Mode of action of Lipopeptides: daptomycin

Daptomycin belongs to the newly discovered bactericidal antibiotics known as lipopeptides and exhibit in vitro ability to swiftly kill practically every gram positive organism that is clinically relevant through mechanism of action that has distinction from the antibiotics that are currently present at markets (Thorne and Alder, 2002). Mechanism of action behind the daptomycin is that it relies on calcium-dependent compound insertion in the cell membrane of bacteria. Understanding the daptomycin structure in the absence and presence of the calcium ions made possible to understand this process in a better way (Jung *et al.*, 2004). Binding of the calcium among daptomycin two aspartate residues results in the decrease in the net negative charge of it and cause hydrophobic surface area to increase, making it possible for a better interaction with the membranes. Additionally, calcium ions encourage daptomycin to insert deeper in the membrane via bridging residual amino acids on the daptomycin with a negative charge and phospholipids also carrying a negative charge which are usually located in plasma membrane of the gram-positive pathogens. The true mechanism resulting in the death of the bacteria by the deeper insertion in the plasma membrane is debatable.

Movement of the ions has been shown to be caused by daptomycin across the cellular membranes, induction of the potassium efflux in the *Bacillus megaterium* and *S. aureus* is evidence of it (Allen *et al.*, 1987) and interaction that is dependent on the calcium with the planar bilayer membranes (Lakey and Lea, 1986) and the phospholipid vesicles (Lakey and Ptak, 1988). Thus, it is proposed that action of daptomycin effects that depend on calcium by which a phenomenon called depolarisation takes place, where dissipation of transmembrane electrical potential gradient occurs. (Allen *et al.*, 1991).

Maintaining a plasma membrane which is appropriately energized is essential for the bacterial growth as well as its survival (Alborn Jr *et al.*, 1991), but depolarisation in itself in not a lethal action, as

valinomycin, results in the depolarisation via potassium ions infers a bacteriostatic effect. Nonetheless when the proton motive force is absent, of which transmembrane electrical potential gradient is the primary component, cells lose their ability to take up the required nutrients for the growth or create ATP. Electrochemical gradient collapse might be the explanation behind the contrasting effects inferred by the daptomycin such as RNA, lipoteichoic acid, lipid biosynthesis, DNA and peptidoglycan inhibition in the *S. aureus* (Canepari *et al.*, 1990), or such events might be the independent consequences of the action of daptomycin.

Mechanism of action of different antibiotics for gram negative bacteria

Gram-negative microbes usually show more resistance to the antibiotics compared to the gram positive bacteria, explanation of which can be given as gram negative bacteria having an outer wall barrier of permeability that keeps in check the entry of antimicrobial compounds into the cell (Vaara, 1992) whereas efflux systems that are broadly specific accommodate numerous structurally unrelated antimicrobial compounds, which might include dyes, antibiotics, fatty acids, biocides, detergents, homoserine lactones, and organic solvents (Poole, 2000; Poole, 2001; Poole, 2002). Restricting the entry of the drugs while actively excreting the drug causes drug accumulation to get limited, thus incurring a protective effect for the bacteria and preventing any detrimental effects of such agents. Furthermore, infections resulting by the gram-negative bacteria are posing a huge challenge concerning the emergence of drug resistance in these pathogens. Multidrug resistance (MDR) as well as extensively drug resistance (XDR) makes most effective of the drugs to fail (Magiorakos *et al.*, 2012). One of the major threats to the health of the human beings is resistance to drugs. Bacteria that produce AmpC beta-lactamases, carbapenemase, and extended-spectrum beta-lactamases (ESBLs) are emerging as a challenge in terms of therapy. Organisms which incur the highest risk have been grouped together under a collective term known as "ESKAPE", which translates as *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Enterobacter* species, due to the ability of these microbes to escape the detrimental effects of the antimicrobial compounds (Boucher *et al.*, 2009).

The coming portion presents a summary of crucial antimicrobial compounds that are being used nowadays as well as new drugs that are being studied for the treatment of gram-negative bacteria.

Drugs such as rifampicin, polymyxins, Fosfomycin and temocillin were used to treat infections in the past and have now been revived to treat gram negative infections.

Polymyxins

Rise of the MDR gram negative bacilli such as *P. aeruginosa, K. pneumoniae and A. baumannii*) along with absence of the newer antimicrobial agents caused revival of the polymyxins, as polymyxins are older class cyclic polypeptide antimicrobial agents which was discovered from *Bacillus polymyxa* in 1947 (Falagas *et al.*, 2005; Li and Nation, 2006). They are comprised of polymyxins A to E, and only polymyxin B and E (colistin) are available in the market currently.

There are two available forms of colistin: colistin sulfate (in the form of powder for using topically and in the form of syrup or tablets for the decontamination of the bowel) and secondly as colistin methane sulfonate (colistimethate sodium; CMS) to be administered in a parenteral way.

Colistin target the cell membrane of the bacteria on the point where polycationic peptide ring makes an interaction with lipopolysaccharide lipid A, permitting the penetration via outer membrane through displacement of the Mg^{2+} and Ca^{2+}. Insertion among the cytoplasmic membrane phospholipids causes integrity of the membrane to lose subsequently leading to the death of bacteria (Falagas *et al.*, 2005; Giamarellou, 2006).

Fosfomycin

FOM is broadly active against numerous gram-positive as well as some of the gram-negative bacteria as it blocks off the synthesis of the cell wall irreversibly at the earlier stage compared to the beta-lactams or the glycopeptide antibiotics. FOM leads to the inhibition of peptidoglycan synthesis initial step that is triggered by the uridine diphosphate N-acetyl-glucosamine-enol-pyruvyl-transferase along with its co-enzyme called as phosphonole-pyruvate. The action of the target is performed inside the cytoplasm of the bacteria (Hendlin *et al.*, 1969; Kahan *et al.*, 1974).

FOM used either of two pathways of active transport to gain entry into the cell. The facultative system of hexose-monophosphate transport system (uhpT) has its dependence on G-6-P presence which is an inductor of extracellular hexose monophosphate.

Different species of the bacteria like *Staphylococcus, Salmonella, Klebsiella, Enterococcus, Shigella* and *Enterobacter* uses this mechanism of transport. The secondary pathway L-α-glycerophosphate transport system (glpT), is induced by glycolysis intermediate, that is glyceraldehyde-3-phosphate (Lin, 1976).

Tigecycline

In the middle of the 1990s, a newer analogs of tetracycline were investigated for the activity against bacteria that are resistant to tetracycline (Tally *et al.,* 1995). Adding an N-N dimethylglycylamido (DMG) group to the minocycline D ring's 9th position gave rise to first glycylcyclines called, tigecyclines (GAR-936) (Sum *et al.,* 1994; Sum and Petersen, 1999; Tally *et al.*, 1995). This structural change permits binding of the tigecycline to target site of the ribosomes as well as allows it to escape majority of resistance mechanisms against tetracycline that are encoded by tet gene. This causes tigecycline to show greater activity against broad range of bacteria that are resistant to tetracycline.

Entry of the tigecycline into the bacterial cell is via passive diffusion method or via routes of active transportation. Resembling the tetracyclines as well as the structural analogs in the cytoplasm, it binds reversibly to the 30S ribosome subunit thereby blocking the biosynthesis of the proteins subsequently halting the bacterial growth (Chopra and Roberts, 2001; Bauer *et al.*, 2004).

In majority of the bacteria the effect incurred is bacteriostatic rather than bactericidal. Translation mediated via tigecycline is inhibited same as tetracyclines by interference of aminoacyl-tRNA accommodation in A site of the ribosome, that precedes reaction of peptidyl transfer (Bauer *et al.*, 2004; Chopra and Roberts, 2001; Olson *et al.*, 2006). Most notably, there is 5 folds increased binding of the tigecycline to the high affinity sites of the ribosomes compared to the tetracyclines even though the orientation is different (Chopra and Roberts, 2001;Bauer *et al.*, 2004; Olson *et al.*, 2006).

The data regarding the structure of complex of ribosome and tigecycline is still lacking even though 3D model of 30S ribosomal subunit of *T. thermophilus* bound with the tetracycline as shown by the x-ray crystallography demonstrated location of Tet-1 (binding site 1 with high affinity) to be between shoulder as well as head of 30S subunit that is proximal to the 16S rRNA helix 34 as well as the A site (Brodersen *et al.*, 2000).

The 16S rRNA phosphate backbone oxygen atom react with tetracycline's hydrophilic part via many interactions of the hydrogen bonding as well as Mg^{2+} coordination that are bound to the molecule of the tetracycline. From the data regarding the structures, binding of the tetracycline is proposedly shown creating steric hindrance preventing aminoacyl-tRNA from the rotation of in the site A for the reaction of peptidyl transfer (Brodersen *et al.*, 2000). Tigecycline is thought to have a same mode of the action.

Aminoglycosides

Even though aminoglycosides are not a newly found class of antimicrobials, they are clinically thought to be a valuable asset against the infections. They are

effective against a broader range of the organisms such as aerobic bacteria, as well as mycobacteria and several gram-negative bacteria mycobacteria. They show particular potency against the bacteria belonging to family Enterobacteriaceae, including *K. oxytoca*, *E. aerogenes*, *Proteus* spp., *Serratia* spp., *Escherichia*, *Providencia* spp., *Morganella* spp., and *Klebsiella pneumoniae*(Ristuccia and Cunha, 1985; Aggen *et al.*, 2010; Landman *et al.*, 2010). This class of the drug also exhibit good activity the *Staphylococcus aureus*, isolates of *P. aeruginosa* that are resistant to both vancomycin and methicillin and to some extent against *Acinetobacter baumannii* (Ristuccia and Cunha, 1985; Aggen *et al.*, 2010; Landman *et al.*, 2011).

Inhibition of protein synthesis takes place when aminoglycosides bind in high affinity with 16S ribosomal RNA, A site of 30s ribosomes (Kotra *et al.*, 2000).

Even though members of the aminoglycoside class have a varied specificity for the various regions on site A, they all result in alteration in its conformation. This interaction results in antibiotic promoting mistranslation via induced misreading of the codon on aminoacyl tRNA delivery. This causes errors to arise in the protein synthesis, permitting incorrect assembly of the amino acids into polypeptides which is afterwards released causing damaging to plasma membrane as well as elsewhere (Davis *et al.*, 1986; Mingeot-Leclercq *et al.*, 1999; Ramirez and Tolmasky, 2010; Wilson, 2014).

Some of the aminoglycosides also have an impact on the synthesis of the proteins via blockage of the elongation or inhibition of the initiation altogether (Davis, 1987*; Kotra et al.*, 2000; Wilson, 2014). The actual mechanism behind the binding followed by downstream effects is different due to the chemical structure, but all the aminoglycosides are swiftly bactericidal (Davis, 1987; Mingeot-Leclercq *et al.*, 1999).Entry of the aminoglycosides is completed in three particular stages, in the first step bacterial membrane permeability is increased, while second and third stages both depend on the energy.

In the first step, polycationic aminoglycoside binds electrostatically with bacterial membrane components that are negatively charged like teichoic acids, phospholipids, LPS after magnesium ions are displaced (Davis, 1987; Taber *et al.*, 1987; Ramirez and Tolmasky, 2010).

Bacterial membrane lipid components stabilization as well as cross bridging is resulted by the cations and removal of them causes outer membrane to be disrupted subsequently causing permeability to enhance and initiating uptake of the aminoglycoside (Hancock *et al.*, 1981; Hancock, 1984; Hancock *etal.*, 1991; Ramirez and Tolmasky, 2010).

Entrance into the cytoplasm through a process that is mediated by the electron transport, depends on energy and is slow (Kislak, 1972; Martin *et al.*, 1972; Davis, 1987;Taber *et al.*, 1987). Protein synthesis is inhibited, and protein mistranslation takes place once the molecules of aminoglycosides gain cytoplasmic access. Insertion of these mistranslated proteins into the plasma membrane results in damaging it while also allowing more aminoglycosides to enter (Davis *et al.*, 1986; Nichols and Young, 1985). This results in rapid uptake of any additional molecules of aminoglycosides into cytoplasm, increase in the protein synthesis inhibition, mistranslation, as well as accelerating death of the cell (Davis *et al.*, 1986; Davis, 1987; Taber *et al.*, 1987; Ramirez and Tolmasky, 2010).

Antibiotic resistance and its basic mechanisms adapted by the bacteria

Antibiotic resistance can be defined as capability of any bacteria to make certain changes in itself to avoid detrimental effects of the drugs – “that is, the germs are not killed, and their growth is not stopped” (Centers of Disease Control and Prevention, 2021). Antibiotic resistance rise translates to loss of inexpensive and effective treatment of the simple infections (WHO, 2018), driving us towards an era when antibiotics were not a thing (WHO, 2014). It is

estimated that in 2050, 10 million people are subject to death directly resulting due to antibiotic resistance, that is higher than the number of deaths resulting due to cancer or accidental deaths due to traffic (Lancet, 2009). Antibiotic resistance is becoming one of the most threatening crisis of the public health in the world. Use of the antibiotics is the primary cause behind the rise in the resistance (Davies and Davies, 2010; Miller *et al*., 2014;Holmes *et al*., 2016). In the healthcare, using antibiotics inappropriately like when the benefits are either inexistent or minimal contributes in increased rates of resistance (Kothari *et al*., 2013).

Rise of the resistance is credited either to the mutations or to the selective growth in the presence of gradually increasing antibiotic concentrations or by acquiring foreign determinants of the resistance. Resistance can take vertical routes of dissemination or via the resistant clones like demonstrated by global spread of methicillin-resistant *Staphylococcus aureus* (MRSA), or it can spread horizontally via intra and inter species transfer of specific genes by i) transformation, ii) transduction and iii) conjugation.

Transduction is a bacteriophage mediated process and restricted to a narrow range of hosts i.e., to particular species. Conjugation covers a wide range of the organisms encompassing even the gram barrier, requiring direct contact between cells as well as conjugative elements presence. Lastly, strains show transformations that are conventionally competent such as *pneumococci* that are capable of taking in the naked DNA from the surrounding environment. This permits remodeling of the sequences of the DNA via exchange of the DNA cassettes resulting in the mosaic gene formation.

Antibiotic resistance mechanism involves interference with the action of the molecule of antibiotic or preventing it altogether. Bacterial cells possess numerous strategies, and it sometimes happen that a single mechanism works against an identical antibiotic. General mechanism behind the resistance is (I) reducing antibiotic concentration in the cell by either enhancing the efflux or preventing its uptake. Reduction in the antibiotic uptake can be achieved for example via deleting membrane porins via which antibiotics gain entry into the cell (Nikaido, 2001; Nikaido, 2003). AcrAB-TolC is an unspecified efflux pump located across the whole membrane of numerous clinically important gram-negative bacteria and are responsible for transporting huge variety of the toxic materials including different antibiotics such as chloramphenicol, ciprofloxacin, and tetracycline. Genetics changes that result in the overexpressing the pumps subsequently cause resistance to increase (Baucheron *et al*., 2004; Keeney *et al*., 2008; Swick *et al*., 2011). Another common strategy employed is (II) prevention of the binding of antibiotic to its specified cellular target. This is achieved by causing alteration to the target molecule's binding site for the antibiotic via enzymatic activity or mutation (Brandis *et al*., 2015; Hooper, 2000), or via protective molecule presence which competes in binding with the antibiotic (Connell *et al*., 2003) or via destruction or alteration of antibiotic molecule by the enzymes (Bonnet, 2004; Robicsek *et al*., 2006). Resistance to both quinolones as well as rifampicin is acquired via mutations in cellular target, DNA gyrase and RNA polymerase, inhibiting antibiotic molecule binding (Brandis *et al*., 2015; Heisig and Tschorny, 1994; Marcusson *et al*., 2009; Piddock *et al*., 1999; Telenti *et al*., 1993). Proteins responsible for the protection of ribosomes like TetM serves to protect from binding of the tetracycline (Connell *et al*., 2003; Dönhöfer *et al*., 2012) whereas resistance against fluroquinolone antibiotics is conferred by proteins for topoisomerase protection (Tran *et al*., 2005; Garoff *et al*., 2018). Mechanism of resistance against important beta-lactams is inferred by the beta-lactamases which destroy the antibiotics (Bonnet, 2004). Moreover, the cell (III) takes measures to bypass the detrimental effects of the antibiotic.

This is usually done by deserting target molecule usage through finding alternate proteins for performing similar biochemical functions like target molecule or via increased expression of target molecule. An example pertaining the alternate protein

is resistance mediated via MecA in MRSA (Stapleton and Taylor, 2002) as well as MurA overexpression, which is targeted by fosfomycin can cause resistance of clinical levels (Couce *et al*., 2012).

Thepathways may differ in their extent depending upon different types of resistance, different kinds of the bacteria as well as on the variety of the environments and locations (Woolhouse and Ward, 2013).

Classification of antibiotics into different generations due to antibiotic resistance

The effect of the antibiotics has not been on the treatment of the infectious disease only but on the society by introducing a change in the mortality as well morbidity. From the time when the first antimicrobials were introduced (1911), there has been discovery of numerous new drugs which provided clinicians with various therapeutic opportunities for the diseases that were previously thought of as life threatening. Nonetheless, using antibiotics in an unrestricted manner has given rise to a newer era where clinicians are facing the pathogens which are resistant to these antibiotics (Zaffiri *et al*., 2012). Bacterial infections resistant to the drugs are escalating at a continuous phase and becoming a problem which threatens the health of the public significantly and there is dire need of developing newer strategies to fight them off (Worthington and Melander, 2013).

β-Lactams are among the three major classes of the antibiotics (Fisher *et al*., 2005), and action mechanism as well as the history of beta lactams have gone through extensive reviews (Burger, 2003). B-lactams are counted among one of the most successful of the drugs for treating infections caused by different species of bacteria for past six decades (Coleman, 2011), but the increase in the clinical resistance is the problem that plagues it. B-Lactams mimic the naturally found substrate called D-Ala-D-Ala from the penicillin-binding proteins (PBP) family of the enzymes that are crucial for the cross-linking of peptidoglycan component found in the cell wall of the bacteria for exerting their antibiotic effects (Tipper and Strominger, 1965). A complex of acyl and enzyme is formed by the B-Lactams with the PBPs, thus transpeptidation activity is inhibited as well cell wall integrity is disrupted that subsequently leads to lysis of the cell (Lee *et al*., 2001). Modifying the PBPs is a well-established strategy behind the enterococci, pneumococci and MRSA resistance (Mulligan *et al.,* 1993; Kaplan and Mason Jr, 1998). B-lactams have numerous classes such as monobactams, penicillins, carbapenems, and cephalosporins (Worthington and Melander, 2013).

Classification of penicillins

All of the members from the class penicillin are 6-aminopenicillanic acid derivatives containing a structure of beta-lactam ring which is critical for the antibiotic activity (Rolinson, 1979). Penicillin classification is dependent on base of the extra chemical substitutes which are linked on the side chains that induce changes in the activity spectrum and the bioavailability extending all the way towards gram-negative bacteria in comparison with penicillin G. Based on the activity spectrum there are four different classes of penicillin: very-narrow-spectrum (penicillin resistant to penicillinase), broad-spectrum penicillin or the antipseudomonal penicillins, narrow-spectrum penicillin or natural penicillin, and extended-spectrum penicillins or aminopenicillins (Zaffiri *et al.,* 2012). Development of newer types of the penicillin is driven by resistance emergence. Beta-lactam ring getting cleaved is the major action taken for the resistance by the bacteria (Gold and Moellering Jr, 1996). Penicillinases belong to particular group of the enzymes belong to the family of beta-lactamases that are capable of hydrolyzing beta-lactams ring. Their identification was done initially in the 1940 in the strains of E.coli but a rapid spread has been observed in other bacteria (Abraham and Chain, 1988).

Penicillin V (1944), benzathine penicillin (1954), penicillin G (1945), and procaine penicillin (1947) all belong to group of narrow-spectrum penicillin. Gram positive rods and cocci as well as gram negative cocci

show susceptibility against penicillin G along with the anaerobes. Sadly, using penicillin G widely following its introduction has led to the production of resistant bacterial strains (Finland *et al.*, 1950;Eickhoff *et al.*, 1965; Lowy, 1998; Whitney *et al.*, 2000). The quick emergence of the staphylococci which was resistant to the penicillin provided drive for the research for other alternatives. During the late 1950s, a semi-synthesis surrounding the 6-aminopenicillanic acid gave birth to newer class of penicillin that was resistant to penicillinase: dicloxacillin, methicillin, cloxacillin, and oxacillin (Donowitz and Mandell, 1988; Rolinson, 1979; Rolinson *et al.*, 1960). Their use is only for the methicillin-sensitive *Staphylococcus aureus* (MSSA). It is crucial that activity spectrum is very narrow and give rise to MRSA strains (Barber, 1961; Jarvis *et al.*, 2007).

Amoxicillin as well as ampicillin are counted among the first of the antibiotics belonging to broad spectrum or second-generation penicillins. Introduction of the ampicillin was done so that gram-negative bacteria can be covered in a better way, but it was found out soon that these organisms demonstrate varied susceptibility. They demonstrated similar chemical structure but serum concentrations in higher level was showed by amoxicillin upon the oral administration (Brogden *et al.*, 1975). Second-generation penicillins demonstrate activity against numerous bacteria including strains of *Bacillus anthracis,* enterococci, streptococci, staphylococci, *L. monocytogenes,* and *Clostridia spp* which were non-penicillinase producing. Talking about gram negative bacteria these penicillins show activity against *Shigella, H. influenzae*, *Salmonella* and *E.coli* (Maiti *et al.*, 1998). Amoxicillin (1972) shows efficacy against numerous pathogens and is regarded as preferred drug for the treating numerous infections (Ronald *et al.*, 1977;George *et al.*, 1990; Shvartzman *et al.*, 1993;Alary *et al.*, 1994; Huang *et al.*, 1998;D'Elios *et al.*, 1999; Deeks *et al.*, 1999; Dowell *et al.*, 1999; Lorber, 1997; Workowski *et al.*, 2002).

Tircacillin (1971), piperacillin (1977), and carbenicillin (1957) represent penicillin's next generation. These antibiotics are labelled as extended-spectrum antibiotics and demonstrate activity against gram negative bacteria, cocci of gram positives and anaerobes. Furthermore, chromosomal beta-lactamases are resisted by these drugs like as produced by *Pseudomonas aeruginosa* as well as *Enterobacter* species. In 1995 there was introduction of the combination called piperacillin- tazobactam (1989) and is possibly the mostly used one owing to its activity against gram-positive bacteria as well as enterococci and streptococci. Nonetheless, this combination favored mainly due to its activity against *P. aeruginosa* and other gram-negative bacilli(Sanders Jr and Sanders, 1996).

Different generations of cephalosporins

On the chronological order, cephalosporins are presented as the class that was discovered and developed secondly following the discovery of penicillins. Cephalosporins have a chemical structure where the beta-lactam ring is conjugated with the 6 membered ring that contains nitrogen atom and sulphur (Darville and Yamauchi, 1994). Being ß-lactam antibiotics, cephalosporins have bactericidal activity and interference in the synthesis of the cell wall is their major mode of action.

There is variability in the individual activity of the cephalosporins and can get affected via numerous factors such as their capability of resisting enzymatic degradation as well as ability of penetrating the cell wall of the bacteria. There are five different groups of the cephalosporins on the basis of their activity spectrum against both gram negative and gram-positive bacteria as well as temporal discovery.

First generation cephalosporins

Cephradine, cefazolin, cefadroxil, cephalothin, cephalexin, and cephapirin are counted among the first generation of the cephalosporins.

The first generation of the cephalosporins show activity against cocci of gram positives like *streptococci spp* and *staphylococci spp* while they show minimal coverage against the gram-negative

bacteria. Gram negative bacteria showing highest susceptibility against the first generation of cephalosporins are *Klebsiella pneumoniae, Proteus mirabilis, E coli,* and *streptococci spp.*

There is usually prescription of first generation of cephalosporins via oral route for the uncomplicated issues of the soft tissue and skin like cellulitis as well as abscesses commonly occurring because of the infection by *Staphylococci spp* and *Streptococci spp.* (Bergeron *et al.*, 1973; Hsieh and Ho, 1975).

Second generation cephalosporins

The division of second generation cephalosporins into two different subgroups: the second generation as well as the cephamycin subgroup. among the second-generation subgroups some are cephprozil and cefuroxime while the cephamycin subgroup consist of cefoxitin, cefmetazole, and cefotetan. In the first group cefuroxime shows increased coverage against the *H. influenzae.* Indication for it also consist of in both children and pregnant women for the Lyme disease. The subgroup cephamycin shows greater coverage for *Bacteroides* species. Gram positive cocci are less susceptible to second generation cephalosporins compared to 1st generation cephalosporins but show greater activity against bacilli of gram negative. They are usually prescribed for the treatment of respiratory infections like pneumonia or bronchiolitis. Moreover, Other than providing coverage against the bacteria which first generation cephalosporins show activity against second generation cephalosporins also cover *Neisseria* species, *Serratia marcescens, H. influenza* and *Enterobacter aerogenes*(Tartaglione and Polk, 1985). It is notable that, cefuroxime is the only second generation cephalosporin which crosses the BBB and is utilized in the treatment of meningitis (Schaad *et al.,* 1990).

Third generation of the cephalosporins

Ceftazidime, cefotaxime, cefixime, ceftriaxone, cefpodoxime, and cefdinir are all counted among third generation of the cephalosporins. Third generation of the cephalosporins show extended bacterial coverage against gram negative bacteria and are used generally to treat the infections caused by gram negative bacteria which are resistant to both the first- and second-generation drugs as well as other beta lactam drugs. When given intravenously penetration of the blood brain barrier is achieved by the third generation cephalosporins and coverage of the bacteria is done in CSF particularly by cefotaxime as well as ceftriaxone. Administration of ceftriaxone is done for the treatment of meningitis that is caused by *Streptococcus pneumoniae, H. influenza* and *Neisseria meningitidis* or it can be used for the treatment of both the Lyme disease and gonorrhea. Importance of ceftazidime is its activity against *Pseudomonas aeruginosa* (Klein and Cunha, 1995).

Fourth generation of cephalosporins

Cefepime belongs to the 4th generation of cephalosporins. It is considered a broad-spectrum antibiotic which can penetrate CSF. The presence of an extra quaternary ammonium group permits their better penetration of the gram negative bacterial outer membrane. Showing similarity to activity of the ceftriaxone and cefotaxime, cefepime shows coverage against MSSA as well as *Streptococcus pneumoniae.* Akin to the ceftazidime, cefepime are very important in terms of their coverage against *Pseudomonas aeruginosa.* Additionally, to gram negative bacteria which are covered by third generation cephalosporins, cefepime can also provide cover against gram negative bacilli which produce beta lactamases. Even though they are effective against gram negative bacteria as well as gram positive bacteria, cefepime is usually kept reserved for systemic infections with high severity in the patients who might potentially have organisms that are resistant to multiple drugs (Okamoto *et al.*, 1994).

Fifth generation cephalosporins

Ceftaroline falls into the category of 5th generation cephalosporins. It is counted among antimicrobials with broad spectrum that can cover numerous gram positive as well as gram negative organisms which are susceptible to it, nonetheless the quality that differentiates it from the other cephalosporins is its

coverage against MRSA. *Listeria monocytogenes* as well as *Enterococcus faecalis* are also covered by ceftaroline. Nonetheless it should be noted that *Pseudomonas aeruginosa* it is not covered by ceftaroline (Zhanel *et al*., 2009).

Antimicrobial Resistance genes in K. pneumoniae

K. pneumoniae has numerous genes which player role in resistance against antibiotics via different mechanisms and a few studies have been conducted which address contribution done by mechanisms of antibiotic resistance to the virulence when the antibiotic pressure is absent.

The resistance determinants for tetracycline, fluoroquinolones, aminoglycosides, and the trimethoprim-sulfamethoxazole are found usually linked on the transferable or the conjugal plasmids which contains the genes that are responsible for extended spectrum beta lactamases (ESBLs) as well as carbapenemase.

ESBLs (for example TEM, CTX-M and SHV) are modified form of broad spectrum beta-lactamases which have the ability to cause hydrolyzation of aztreonam, 3rd generation cephalosporins, and in some cases fourth generation of the cephalosporins as well, additionally to antimicrobial compounds which broad spectrum beta lactamases have the capability to hydrolyze (Surgers *et al*., 2016; Yu *et al*., 2017; Xu *et al*., 2018).

AmpC β-lactamases expression in higher levels gives resistance to similar substrates like ESBLs do, moreover to cephamycins (for example cefotetan and cefoxitin). Some of *K. pneumoniae* strains like isolates of hvKp, show acquisition of the plasmids which contains genes for AmpC β-lactamase (Xie *et al*., 2018; Xu *et al*., 2018).

Furthermore, OmpK36 as well as OmpK35 are two of the porins the expression of which observes downregulation in numerous clinical isolates encompassing strains that produce ESBL and are resistant to carbapenems. By downregulating the OmpK36 and OmpK35, antibiotic influx is limited inside the bacteria (Ardanuy *et al*., 1998; Hernández-Allés *et al*., 1999; Mena *et al*., 2006; Shin *et al*., 2012).

K. pneumoniae along with the other Enterobacteriaceae have an efflux pump known as AcrAB that plays the role in antibiotic resistance (Li *et al*., 2015). When expression of AcrAB is increased it plays a significant role in providing resistance against numerous antibiotic compounds in the clinical isolates (Bialek-Davenet *et al*., 2015; Wang *et al*., 2015) which is in accordance with the huge range of the substrates this pumps play the role in transporting (Li *et al*., 2015). there has been demonstration of numerous regulators which influence expression of *AcrAB* in both *Enterobacteriaceae* and *Klebsiella* (Weston *et al*., 2018). As an example, RamA is a transcriptional regulator for AraC family which plays a role in resistance against tigecycline through upregulating the AcrAB (Rosenblum *et al*., 2011).

Carbapenemases (for example VIM, OXA [class D], KPC [class A], IMP [class B], and NDM) provide resistance against the similar drugs ESBL do, moreover against the carbapenems as well as cephamycins. Spread mediated via transposons (for example Tn4401 for the KPC) is also of great importance. Pertaining to rise in the number of the reports mainly but not only from Asia (Cejas *et al*., 2014; Compain *etal*., 2017; Becker *et al*., 2018;Roulston *et al*., 2018), note acquisition of carbapenemases by strains of hvKp. Acquiring the KPC is the commonest (Cejas *et al*., 2014; Zhang *et al*., 2015; Zhang *et al*., 2016;Wei *et al*., 2016; Zhan *et al*., 2017; Feng *et al*., 2018; Gu *et al*., 2018; Huang *et al*., 2018), but isolates producing both OXA and NDM-1 have also been described (Shankar *et al*., 2016; Mei *et al*., 2017; Becker *et al*., 2018; Liu *et al*., 2018;Roulston *et al*., 2018; Simner *et al*., 2018; Wei *et al*., 2018).

There has been identification of numerous mechanisms that might be involved in resistance

against polymyxins. The concern has been raised by the discovery of resistance gene known as mcr-l on a transferable and stable plasmid which can infer resistance against polymyxins as polymyxins B as well as E (colistin) or the last defense against the pathogenic strains which produce different metallocarbapenemases like NDM-1. Sadly, there are descriptions for this mechanism of resistance by hvKp (Lu *et al.*, 2018). There is another mechanism which facilitates resistance against polymyxins is by increasing expression of PhoP-PhoQ-Arn pathway. Activation of the PhoP-PhoQ causes *arn* operon to overexpress, subsequently resulting in adding the cationic groups into the moieties of phosphate in lipid A. This, consequently, causes negative charge to decrease as well as decreasing the activity of the polymyxins. Getting inserted into the *mgrB,* that is responsible for encoding PhoP-PhoQ regulation pathway suppressor molecule mgrB and infers resistance against polymyxins (Cannatelli *et al.*, 2014). There is data available showing the same mechanism against the polymyxins opted by strains of hvKp (Dong *et al.*, 2018; Huang *et al.*, 2018).

Antimicrobial Resistance genes in S. penumoniae

Resistance against beta lactam drugs in the pneumococci is inferred from mosaic *pbp* genes development which demonstrates reduction in affinity to antimicrobial molecule. Penicillin resistance expression phenotype is caused by modification of genetic structure in either one or sometimes more than one of the PBPs, thus causing reduction in the synthesis of peptidoglycan. the decrease in the binding affinity cause weakening of the cell wall of the bacteria which can subsequently lead to lysis of the cell and eventually cell death. Six of the PBPs have been noted in the *S. penumoniae*. Most of the resistance against beta lactams is presumably related to these three alterations of PBP: PBP1a, 2b and 2x. The association of PBP2a has been seen with decrease in the susceptibility as well as high MICs compared to the PBP2x as well as the PBP2b that confers resistance against beta lactam antibiotics (Smith and Klugman, 1998). Right now, resistance against macrolides in the *S. pneumoniae* is inferred by two major mechanisms: (1) efflux of the antimicrobial compound from bacteria whereas (2) altering the target ribosome. Gene labeled as *mefA* Is usually responsible for induction of resistance considering the former way described. In the past this mechanism was generally regarded as conferring lower resistance level (MIC_{90} of 4–8 µg/mL) (Jenkins *et al.*, 2008). Altering the targeted ribosome via the use of ribosomal methylase which is coded by the gene known as *ermB*. This mechanism is usually associated with conferring higher resistance level (MIC_{90} >32 µg/mL) (Niederman, 2015).

Resistance against the fluoroquinolones in the pneumococci has its origin from altering the binding site for the fluoroquinolone due to collection of the spontaneous mutations in quinolone resistance determinant region (QRDR) of both *par*C as well as *gyr*A. Genetic as well as biochemical studies have demonstrated the mutations responsible for altering the *parC* contributing in the acquisition of resistance against ciprofloxacin but failed to confer resistance against newly developed fluoroquinolones on their own (Esteban fernández-moreira *et al.*, 2000). This QRDR mutation of the parC adds into the risk of consequent mutations that might further lead to enhanced resistance (Lim *et al.*, 2003). Most of the resistance against fluoroquinolones ≥16 µg/ml has its origins from the occurrence of mutation in *gyrA* and *parC* both. Occurrence of mutation in any of these genes provides resistance against newer fluoroquinolones: gemifloxacin, moxifloxacin, levofloxacin, and gatifloxacin (Brueggemann *et al.*, 2002).

The mechanism that is most important for the resistance of *S. pneumoniae* against the tetracyclines is the protection to the ribosome facilitated by tet(O) and tet(M) genes (Chopra and Roberts, 2001; Doherty *et al.*, 2000).

Trimethoprim-sulfamethoxazole (TMP-SMX) is a combination of drugs that was made public in 1968, these drugs have a synergetic effect and work in tandem as well as have their own individual

mechanism for the inhibition of synthesis of folic acid inside the bacteria (Eliopoulos and Huovinen, 2001). Sulfamethoxazole inhibits the enzyme known as dihydropteroate synthetase (DHPS), which plays a critical role in the formation of dihydrofolate from the para-aminobenzoic acid (Hitchings, 1973). In this pathway, dihydrofolate reductase (DHFR) is inhibited by TMP that causes reduction of dihydrofolate into tetrahydrofolate, that is folate's biological active form (Burchall, 1973; Eliopoulos and Huovinen, 2001). If considered as two separate drugs, there have been observed different mechanisms for resistance against SMX as well as TMP. nonetheless as there is transfer of resistance among the two drugs, there is a link of resistance traits among these drugs(Eliopoulos and Huovinen, 2001). Particularly, resistance against trimethoprim occurs via single substitution of the amino acid in the gene that encodes for DHFR in the *S pneumoniae,* which causes compromise a shun in the trimethoprim binding and leaving DHFR functionally intact. Repetition regarding one or two of the amino acids in the chromosomal dihydropteroate synthetase causes *S. pneumoniae* to become resistant against sulphonamides (Widdowson and Klugman, 1999).

Antimicrobial Resistance genes in N. Meningitidis

N. meningitidis is regarded as a pathogenic bacteria which has a natural transforming capability with population structure defined as 'panmictic' and the characterizing feature is horizontal gene transfer (Maiden, 1998). Furthermore species of Neisseria that are closely related carry plasmids that are related with resistance against antibiotics that are be mobilized to the meningococci (Bäckman *et al.*, 2000), introducing resistance against antibiotic. Lastly, occurrence of the point mutation in the target genes of the chromosome serves as an extra mechanism for acquiring resistance against the antibiotic (Nolte, 1997).

Sulfonamides prove a competitive inhibitor of the DHPS that are responsible for catalyzing the dihydropteroic acid formation on the pathway of folate synthesis inside the bacteria. Resistance against sulfonamides in the *N. meningitidis* is facilitated by the alteration of *dhps* form in the chromosome. Due to this, DHPS loses the capacity to bind with sulfonamides. there are descriptions of two different type of genes that are responsible for resistance in the *N. meningitidis* one of them being found frequently with conventional six base pair insertion that is known to cause reduction in the affinity for sulfonamides where is the other one is the less commonly observed form that lack six base pair insert (Rådström *et al.*, 1992). A suggestion has been given that these determinants of resistance against sulfonamide might have a appeared due to them combining with different species (Fermer *et al.*, 1995), but it is also suggested that they maybe mutant variants of *dhps* genes found in the wild type organism as in the case of a different species of the bacteria (Lopez *et al.*, 1987).

From the time of the first reports of meningococci that is resistant to sulfonamide, there has been recommendation of use of rifampicin on a wide scale for chemoprophylaxis of the meningococcal disease (MD). Rifampicin has action on the beta subunit that is encoded by *rpoB* gene of the RNA polymerase that is directed by the DNA and cause inhibition of the elongation of RNA chain. occurrence of single point mutation in particular region of *rpoB* gene causes development of the resistance (Nolte, 1997).

Resistance against the tetracycline has numerous descriptions in the meningococci, related to a conjugative plasmid being present with *tet* M determinant insertion (Winterscheid *et al.*, 1994). Isolates of the *N. meningitidis* carrying the plasmid maybe uncommon (Bäckmann *et al.*, 1993) but the determinant of the *tet* M resistance can also get inherited via conjugative events among other species of *Neisseria* (Winterscheid *et al.*, 1994).

Isolates of the meningococci with lower resistance level to the penicillin have been labeled as moderately resistant to the penicillin, with their susceptibility decreased or by some other definitions (Oppenheim, 1997), but nowadays the tendency has tilted towards

referring to them as strains that are moderately susceptible (Pen^{ms}) due to the uncertainty of their clinical significance. Resistance demonstrated by these isolates it's because of partly, to reduction in the affinity of PBP2 (Sáez-Nieto *et al.*, 1992). Alteration in the forms of PBP2 are because of the different sequences of *penA* gene being expressed that encodes for that protein.

Another mechanism to penicillin is through production of β-lactamase. The gene for β-lactamase is located on the plasmid, and at only one instance has it been sequenced (Bäckman *et al.*, 2000) moreover it was noted to share similarities with the gonococcal plasmids pJD5 and pJD4. It was implied by those results that up take off the plasmid may have been from strain of *N. gonorrhoeae* via conjugative transfer (Bäckman *et al.*, 2000).

Antibiotic called as chloramphenicol has been utilized as standard therapy for the MD in the countries that are yet developing (Galimand *et al.*, 1998).

The occurrence of the resistance it's because of the gene known as *catP*, that is it transposon Tn4451 fragment from the *Clostridium perfringens* that has undergone the larger deletion of its total sequence making up 80% (Galimand *et al.*, 1998). Transposons in the strains of *N. meningitidis* that are resistant to chloramphenicol render immobile due to the fact that there has been the loss of genes that are mandatory for the excision.

Antimicrobial Resistance genes in S. aureus

A frequently observed phenomenon in the *S. Aureus* is MDR. Resistance against multiple drugs is one of those phenomenon where pathogenic organisms acquire resistance to numerous chemotherapeutic agents (Nikaido, 2009). Following, is schematic diagram depicting all the methods used for resistance mechanism.

One of the well-known examples is resistance against the methicillin by the *Staphylococcus aureus*. Methicillin-Resistant *Staphylococcus aureus* (MRSA) became highlighted when Methicillin-Susceptible *Staphylococcus aureus* (MSSA) showed adaptation towards a particular gene (methicillin-resistant gene) labelled as MecA that is intervened by the genetic element known as Staphylococcus cassette chromosome (SCC) and transfer of it takes place into MSSA through conjugation or transformation (Horizontal gene transfer).

There have been observations made that plasmid of *S. aureus* that has origins from a different environment of the bacteria had a few avant-garde resistant genes labeled as *vgaC* and *ampA*. the resistance gene known as amp showed resistance against anti-microbial compound known as apramycin whereas *vgaC* resistance gene showed resistance against Streptogramin A (Kadlec and Schwarz, 2009;Feßler *et al.*, 2011).

Going to the higher resistance against the methicillin as well as following drug failure, a huge role was played by vancomycin for the treatment of majority of MRSA infections but gradually due to the long-term use of drug, it became resistant to infections of MRSA. the predicted mechanism of the action is thought to be transfer facilitated by the plasmid among species. Genes labeled as *rpoB, graR, vraS*, and *msrR* were noted to have mutations that were playing role for the bacteria to acquire resistance against the mechanism of the vancomycin (Ito *et al.*, 1999; Matsuo *et al.*, 2013).

Concerning the case of penicillin, penicillinase is encoded by the R plasmid, the gene responsible for carrying enzyme is called as *blaz*, and organisms acquiring resistance against penicillin had this gene that cause inactivation of antibiotic via splitting of the beta lactam ring. Resistance against the fluroquinolones was developed by the *S. aureus* via overexpressing the *NorA* efflux pumps. Similar to that occurrence of the point mutations proves as another way via which organism gains resistance against quinolones. Occurrence of the point mutations on topoisomerase subunits happens. Like point mutation occurrence at the *Gr1A* site in the subunit of

topoisomerase IV as well as in the Gyrase subunit *GyrA* (Gnanamani *et al.*, 2017).

AntimicrobialResistance genes in *H. Influenzae*

The antibiotics, β-lactams, are the drugs of choice to treat *H. Influenzae* infections. *H. Influenzae* utilizes two mechanisms against ampicillin resistance, i.e., 1) the alteration in the PBPs which confer reduced affinity to β-lactams, and 2) the production of a β-lactamase. The dominant mechanism among the two is the production of β-lactamase, which is often encoded by bla_{TEM-1} and by bla_{ROB-1} rarely (Farrell *et al.*, 2005). The strains are termed as β-lactamase positive, ampicillin resistant (BLPAR).

Another mechanism involves the substitution of amino acid in the transpeptidase enzyme called PBP3, which is encoded by *ftsI* gene (Dabernat *et al.,* 2002). Strains which do not produce β-lactamase but are resistant or intermediate to ampicillin are termed β-lactamase negative, ampicillin resistant (BLNAR) or β-lactamase negative, ampicillin intermediate (BLNAI) according to the breakpoints for ampicillin (Hotomi *et al.,* 2007). Strains that are unable to produce β-lactamase but are completely or intermediately resistant to ampicillin are called as β-lactamase negative, ampicillin intermediate (BLNAI) or β-lactamase negative, ampicillin resistant (BLNAR) (Hotomi *et al.,* 2007).

H. influenzae possess intrinsic resistance to ketolides and macrolide-lincosamide-streptogramin B agents which corresponds to *acrA/acrB* gene encodingefflux pump, which is homologous but not same as that of *E. coli* efflux mechanism encoded by *acrAB* genes or other efflux pumps and contribute towards the ineffectiveness of these agents against wild-type strains of this pathogen (Sánchez *et al.,* 1997a; Sánchez *et al.*, 1997b; Peric *etal.*, 2003;Peric *et al.,* 2004; Bogdanovich *et al.*, 2006).

H. influenzae also show resistance to tetracycline which is due to the *tet*(B) gene which encodes for efflux pump and lies on conjugative plasmids (Chopra and Roberts, 2001).

As with other bacteria, the resistance to quinolones in *H. Influenzae* comes through mutations in thequinolone resistance-determining region of the gene which encodes for topoisomerase IV and DNA gyrase (Davies *et al.*, 2000; Nazir *et al.*, 2004; Rodríguez-Martínez *et al.*, 2006).

H. influenzae produces chloramphenicol acetyltransferase (CAT) encoded by *cat* gene which confers plasmid-mediated resistance against Chloramphenicol (Burns *et al.*, 1985; Roberts *et al.*, 1980). The gene is particularly present in the conjugative plasmid which the chromosome can also incorporate (Powell and Livermore, 1988).

Trimethoprim and sulfamethoxazole (either used in combination or alone) perform an antimicrobial activity by interrupting cellular metabolism and replication, as it sequentially blocks the tetrahydrofolate production. In case of normal cellular metabolism, the reduction of dihydrofolate to tetrahydrofolate takes places, aided by the dihydrofolate reductase (DHFR) enzyme (Burchall and Hitchings, 1965). Alterations in the DHFR encoding genes confers resistance to trimethoprim by decreasing the affinity between DHFR and trimethoprim. These genes are often present on transposons or plasmids and have probably been originated from bacteria that are closely related. Among the strains of *H. Influenzae*, trimethoprim-sulfamethoxazole resistance is common and occurs due to increased production of DHFR having decreased trimethoprim affinity (de Groot *et al.*, 1991).

Antimicrobial resistance genes in E. coli

The main target of the fluoroquinolones in the *E coli* is the gyrase of it, that has in total 4 subunits two of which are *GyrA* and the remaining two are *GyrB*. Topoisomerase serve as secondary target inside the gram-negative bacteria. There are four subunits of this enzyme two of them are *ParC* while the remaining two are *ParE*. Majority of the mutations were located inside the QRDR region that is found between *Gln107* and *Ala67* in the *GyrA*, while codons

87 and 83 are the points associated with occurrence of most of the mutations (Hopkins *et al.*, 2005). Occurrence of single mutations in the gene labeled as *GyrA* might confer into the resistance against quinolones but for acquiring resistance against fluoroquinolones there is further requirement of more mutations inside *GyrA, parC* or both. Most of the mutations that occur in *parC*, takes place at 84 and 80 codons (Hopkins *et al.*, 2005).

From the time when determinant of first plasmid facilitated quinolone resistance (PMQR) was identified, by the name of *qnrA1*, in the 1997, It has raised serious concerns on a global scale about the international dissemination of genes of PMQR (Cattoir and Nordmann, 2009; Rodríguez-Martínez *et al.*, 2016). Numerous resistance mechanisms are encoded by the plasmid have been observed such as (i) *Qnr*-like proteins (*QnrD, QnrC, QnrS, QnrA,* and *QnrB*) that provide protection to the DNA from binding of the quinolone, (ii) AAC(6′)-Ib-cr acetyltransferase which causes modification of particular fluoroquinolones like enrofloxacin as well as the ciprofloxacin, and (iii) activated efflux pumps (*OqxAB* and *QepA*) (Rodríguez-Martínez *et al.*, 2016). Resistance against aminoglycosides can be caused by targeted mutations which involve 16S RNA and S5 and ribosomal protein S12 (Fourmy *et al.*, 1998; Griffey *et al.*, 1999; Llano-Sotelo *et al.*, 2009). Nonetheless this proves as a successful strategy in conferring higher levels of resistance. Modifying the sites that are targeted by a minor glycosides can be done via methylation of the G1405 as well as A1408 residues on 16S RNA site A, that leads to high resistance level against netilmicin, tobramycin, amikacin and gentamicin (Griffey *et al.*, 1999). The methylases for 16S RNA consist of *RmtA/B/C/D/E/F/G/H, NmpA* and *ArmA* have their origins from the organisms that naturally produce aminoglycoside as a mechanism of self-defense. (Edwards and Puente, 1998).

MurA enzyme is inhibited by fosfomycin that plays a critical role in the synthesis of peptidoglycan. There are two major mechanisms involved in the resistance against fosfomycin: (i) Occurrence of mutations in *uhpA/T* as well as *glpT* genes that encode for the protein that play a role in up taking of the fosfomycin and (ii) Acquiring enzymes that modify fosfomycin like metalloenzymes *FosX, FosA* and *FosB* or some kinases like *FomB* or *FomA* (Silver, 2017).

Majority of the genes that are like *fos* are located on the plasmid, and it has been observed that plasmids that carry *fos* genes are also carrying extra genes of resistance (Lupo *et al.*, 2018; Wang *et al.*, 2017; Wang *et al.*, 2018) which can cause rise in coselection of resistance against the fosfomycin under selective pressure elicited by other antimicrobial compounds.
According to the nomenclature center for tetracycline resistance gene (https://faculty.washington .edu/marilynr/), nine of genes for tetracycline efflux [tet(E), tet(Y), tet(G), tet(A), tet(L), tet(C), tet(D), tet(J), and tet(B)], two of the tetracycline genes for resistance that encode for ribosomal protection proteins [tet(W) and tet(M)], as well as presence of one gene that encodes for oxidoreductase which causes inactivation of the tetracyclines [tet(X)] has been noted in *E coli*. The main mechanisms of resistance against tetracycline found in the *E. coli* isolated from the animal samples consists of (i) efflux by the proteins in an active manner whereas the proteins were from the major facilitator protein superfamily and (ii) ribosomal protection (Shin *et al.*, 2015).

Resistance against the phenicol in the *E. coli* isolated from the animal origins is facilitated by three main mechanisms: (i) enzymatically in activating the non-fluorinated phenicols via chloramphenicol acetyltransferases that is encoded by cat genes, (ii) causing active efflux of the non-fluorinated phenicols (cmlA genes) or via the non-fluorinated as well as by the fluorinated phenicols (floR genes) through proteins of the major facilitator super family, and (iii) methylation of the target site via rRNA methylase that is included by multi resistance gene known as CFR that provide resistance against five different classes of antimicrobial compounds such as non-fluorinated as well as fluorinated phenicols (Schwarz *et al.*, 2004).

Resistance against polymyxin in the E coli isolates might be associated to the genes that encode for enzymes that modify LPS. Operon pmrCAB encodes three distinct proteins labeled as sensor kinase protein PmrB (also called BasS), phosphoethanolamine phosphotransferase PmrC, and response regulator PmrA (also called BasR) (Poirel *et al.*, 2017). Occurrence of the mutations in the pmrB and pmrA have been demonstrated to play a role in acquiring resistance against isolates of the E. coli that were obtained from the poultry farm in the Spain (Quesada *et al.*, 2015). Nonetheless, majority of the mutations that lead to resistance against polymyxins have been noted in the isolates of the *E. coli* from the humans.

In the month of November in 2016, there was identification of the first polymyxin resistance of the plasmid borne origins. The name this gene was given, was mcr-1 and the product it encodes is called MCR-1 phosphoethanolamine transferase (Liu *et al.*, 2016). MCR-1 production in the *E. coli* results in increase by 4 to 8 folds in MIC of the polymyxins (Poirel *et al.*, 2017). There has been detection of the mcr-1 gene in the isolates of the E. coli but among other genera of the Enterobacteriaceae like Enterobacter, Salmonella, Klebsiella and Shigella (Schwarz and Johnson, 2016).

One particular problem with antimicrobial resistance that affect both animals as well as humans is the presence of the ESBL producing *E.coli* (Chong *et al.*, 2018). These bacteria exhibit resistance against cephalosporins, aztreonam as well as penicillins chiefly by producing SHV, CTX-M and TEM β-lactamases that are encoded via *bla*$_{SHV}$, *bla*$_{CTX-M}$, and *bla*$_{TEM}$ genes respectively.

These genes can either be facilitated by the plasmids or have a chromosomal expression. In between these three genes, CTX-M enzymes turned out to have the most extensive spread in humans as well as animals. CTX reflects the potential hydrolyzing activity of the beta lactamases against the cefotaxime, and they do not show many similarities to the SHV or TEM beta-lactamases (Michael *et al.*, 2015; Shaikh *et al.*, 2015).

Sources of antibiotic resistance in the Environment

Concern regarding the resistance was confined originally to acquiring the resistance by the microbes that resulted in epidemic disease as well as was considered an issue with regards to the strains isolated clinically. Nonetheless, in the years passing by, isolation of bacteria that are resistant to the antibiotics have been done from almost every environment of our planet (Morgan *et al.*, 1976; Marques *et al.*, 1979; McNicol *et al.*, 1980; Goñi-Urriza *et al.*, 2000; Chee-Sanford *et al.*, 2001). This proved surprising to a lot of clinicians due to fact that resistance was observed in the regions which had never been subjected to the human impact. Even after the increase in the awareness of the resistance in the environment, the focus of numerous researchers has yet remained the pathogens which show environmental survivability. It was thought that humans are only endangered by them if the disease caused by them involved antibiotic resistance. For numerous years, the research focused on the environmental resistance showed this particular viewpoint. Nonetheless, it is now known to us that genes inferring the resistance wider and far away compared to what was believed once and that there is development in the pool of resistance regarding the nonpathogenic microbes located in the environment, in animals or in humans (Fredrickson *et al.*, 1988; Wiener *et al.*, 1998). These non-pathogenic microbes prove a source via which pathogenic microbes might acquire genes which confer the resistance, and sequentially, they can get resistant via acquiring resistance genes from the pathogens which they discharge into the environment for example through the sewage (Top *et al.*, 1994) or through the runoff from the agricultural site (Gotz andSmalla, 1997; Jensen *et al.*, 2001). So, dissemination of the bacteria that are resistant proves not a problem only by the resistant microbes themselves but the availability of the resistance genes to the pathogenic microbes through gene transfer is also a major problem. Even though the resistant microbes can naturally be found only in the environment, majority of the resistance is related to the impacts made by the humans, this impact can be agricultural in nature, or any other

impact directly made by humans. Use of the antibiotics by the humans can progress towards environmental resistance through domestic waste discharge, hospital wastewater discharge, and industrial pollution discharge (Harwood *et al.*, 2001; Iversen *et al.*, 2002;Blanch *et al.*, 2003; Schwartz *et al.*, 2003). In addition to that, some of the antibiotics are mixed with the feed given to the animals for the treatment of their infections, as subtherapeutic doses or as prophylactics as the growth promoters (Kelley *et al.*, 1998). Even though there is lack of definitive numbers, some of the authors have made publications and estimate that by the 1980s nearly fifty percent of all the antimicrobial agents that were being used in the USA were also made part of the feed for the animals (DuPont and Steele, 1987). In 1994 in Denmark, vancomycin weighing only 24 kg was used for the treatment of the infections in the human population compared to animals where 24,000 kg was used (Witte, 1998). According to the study by Levy(Levy, 2001), in the USA in 1998, 25 million pounds of the antibiotics that was produced was used for the agricultural purposes.

This practice caused rise of numerous bacteria in the gut of the food animals which were resistant to antibiotics. From that point these microbes made their way into the food chain of the humans through contamination acquired during slaughtering, or via environmental discharge of the waste. Observation of the resistance has been made to closely following the use of any of the antibiotics (Aarestrup, 1999).

Using antibiotics in such a manner can result in the emergence of pathogens that are resistant, in higher concentrations as well as non-pathogenic resistant organisms and resistance genes in the whole environment of the farm as well as the nearby surrounding environments which can get affected through the runoff from the farms. As discussed later, once there is a spread of the resistant microbes into the environment, a health risk is posed by them if there is their colonization or if there is dissemination of the resistance genes to the microbiota which colonize the humans.

Hospital effluents

Antibiotics that are utilized in the medicine for treating infections as well as prophylactically are chiefly released un-metabolized in the aqueous bodies through the wastewater. The effect is given off by the presence of the active compound. Sometimes therapeutic drugs which are not used are thrown in the drains. Among the compounds that are active in the hospital effluent, there are also antibiotics as well as disinfectants (Kümmerer, 2001). It was found by (Schwartz *et al.*, 2003) that there are vanA genes which are carried by the bacteria in the effluent from the hospital. The gene coding for the resistance against the methicillin called MecA that staphylococci was found only in the wastewater from the hospital and not found the in the wastewater of the municipal waste (Heuer *et al.*, 2002). Observation of the genes giving resistance against gentamycin were noted in *Enterobacteriaceae* as well as *Acinetobacter pseudomonas* in the sewage from the hospital waste (Heuer *et al.*, 2002).

Input of resistant bacteria into the municipal sewage

Hospitals are presumed as the crucial source of inputting the bacteria that are resistant into the municipal wastewater. The number of bacteria observed in the ICU effluent were found to fall in the same range as the municipal sewage treatment plants (STPs) influent (Hingst *et al.*, 1995). Considering that hospital effluent dilution via the municipal sewage is usually greater than a 100-fold (Kümmerer and Henninger, 2003) and also considering the fact that resistant bacteria are found anyways in the municipal waste (Hingst *et al.*, 1995) due to antibiotics use at the home level and it can be concluded that the general population plays a key role in the input of the resistant bacteria in the STPs. Another point can be made that in Germany only one fourth of all the antibiotics usage can be associated with the hospitals (Kümmerer and Henninger, 2003). Considering that the effluent from the hospital participates makes up <1% of the whole municipal waste, it becomes logical that hospitals are not the chief source of the resistant bacteria in the municipal waste. Situation might present differently for MDR bacteria. Presumably,

selection of the MDR bacteria takes place in the hospitals from where they are discharged and made part of the wastewater (Römling *et al.,* 1994). There was a correlation observed between the amount of MDR bacteria in the municipal sewage with number as well as size of the hospitals that were connected to the STP. It was noted that numbers as well as the types of bacteria that showed resistance isolated from the fully working and operational hospital effluent fall into the same range to that of influent of STP (Hingst *etal*., 1995). A study by Reinthaler *et al.* (2003) noted that STP that received municipal waste containing effluent from the hospitals showed highest rates of the resistant microbes.

Municipal sewage and activate sludge of STPs

Disinfectants as well as the antibiotics have been observed in the water from sewage at the concentrations that there were few microbes for every liter. There is presence of resistant microbes in the anaerobic digestion process, municipal waste as well as the aeration tanks in the processing of sewage treatment plants (Römling *et al*., 1994; Heuer *et al*., 2002; Schwartz *et al*., 2003). Reinthaler *et al.* (2003) along with the other co-workers researched on resistance of the *E.coli* in three treatment plants for sewage in Austria against 24 antibiotics via classical method i.e., isolation followed by cultivation and then resistance testing. It was seen that *E.coli* is resistant to numerous antibiotics like penicillins (piperacillin, ampicillin), trimethoprim/sulfamethoxazole, quinolones (nalidixic acid), cephalosporins (cefuroxime, cephalothin) and tetracycline. Resistant as well as MDR bacteria which are pathogenic in nature like *Acinetobacter spp*. (Heuer *et al*., 2002) have been seen in the STPs as well as the wastewater and noted in the transfer of the resistance (Römling *et al*., 1994; Marcinek *et al*., 1998; Kümmerer and Henninger, 2003). There have been reports of gene exchange among the *E.coli* and *pseudomonas* in the sewage sludge (Schwartz *et al*., 2003).

Surface water

Bacteria which are resistant to the antibiotics have been found in the surface water samples (Muela *et al*., 1994; Marcinek *et al*., 1998). Goñi-Urriza *et al.* (2000) found in their study a correlation among the resistant bacteria in the input of urban water as well as in the rivers. Schwartz *et al.* (2003) successfully amplified genetic sequences for AmpC beta lactamase via PCR in the surface water. There have been reports of generic transformations in the *E.coli*(Baur *et al*., 1996).

Ground water

Surprisingly, higher incidence of resistant *E.coli* has been reported in the rural ground water samples (McKeon *et al*., 1995). There is lack of speculation of the authors regarding the origins of the resistance but the manure runoff either from the farms or any leakages from the septic tanks provide a clear possibility in the inputting of bacteria in the ground water. Broken sewage pipes might also play a role.

Drinking water

Detection of bacteria resistant to the antibiotic was done from 1980s to the 1990s (Armstrong *et al*., 1981; Al-Ahmad *et al*., 2000). These authors noted the identification of the resistant bacteria via the classical methods of microbiology such as standardized plate counting, took place inside the drinking water distribution network system.

They reached the conclusion that raw water treatment as well as the consequent distribution puts a selective pressure for the development of` antibiotic resistance in the bacteria. In concurrent with the data, increased phenotypic rate of resistance were also noted for the samples of drinking water points in the study conducted by Schwartz *et al.* (2003). It was noted by the authors that there was presence of AmpC and vanA genes in the heterotrophic bacteria found in the biofilms of the drinking water. Enterococci were absent from the samples. It was concluded by the authors that this is the indicator of the probable transfer of resistance to the autochthonous bacteria.

Sediments

Presence of resistant bacteria might be due to application of the antibiotics in the fish or due to

selection by antibiotics which are found in the sediments. Bacteria showing resistance to antibiotic compounds have been observed in the sediments. Andersen and Sandaa (1994) and Samuelsen *et al.* (1992) extracted and isolated gram-negative bacteria resistant to tetracycline from the unpolluted as well as the polluted marine sediments. Increase resistance to the antibiotics in the bacteria found in the sediments serves usually as the most delicate indicator, indicating that antibiotics have been used in the past.

Soil

Use of the antibiotics for the veterinary purposes or simply as substance that promote growth are excreted out by the animals and often end up in form of manure along with the disinfectants that are used in the livestock. The use of the manure happens in the form of the fertilizers in the agricultural land. If there is use of the antibiotics in the animal husbandry, they pass out in the soil from the manure. Concentrations up to 0.3mg per kg of tetracyclines have been noted in the soil (Kümmerer, 2001). Soil has strong absorption for some of the sulphonamides, quinolones, and tetracycline (Marengo *et al.*, 1997; Tolls, 2001Golet *et al.*, 2002; Hamscher *et al.*, 2002;De Liguoro *et al.*, 2003;Gavalchin and Katz, 2020). Pang *et al.* (1994), in their study, noted mycobacterium acquiring a gram-positive resistance gene against the tetracycline in a test conducted in the laboratory. This is among the few reported cases indicating a probable transfer of gene among the bacteria found in the soil and bacteria found in the intestine of the humans. Lorenz and Wackernagel (1994) also demonstrated genetic material exchange among the bacteria of the soil. Variations in the amino acid GyrA bacterial subunit are potentially related with the natural resistance against the fluroquinolones (Waters and Davies, 1997).

Spread and evolution of resistance genes in the environment

Resistance against the antibiotics can root from both the mutation in the genomic makeup of the bacteria and from up taking of the foreign DNA. Mutations occur readily and can get fixated in patient or any animal getting treated with any antibiotic. Such strong selection pressure is seldomly found anywhere else. Moreover, this process remains independent from the genetic reservoir in the other species. Thus, environmental conditions externally are usually rare for the provision of the huge contribution to the resistance evolution that is based on the mutation for numerous pathogens. Regarding the uptake of the novel resistance factors, soil, water and the other environments where there the ecological niches observe a vast variability leads to the provision of a gigantic gene pool where the diversity exceeds by far from what is offered by animal and human microbiota (Rinke *et al.*, 2013; Schulz *et al.*, 2017).

It is indeed most striking that environmental microbiota is immensely diverse and provide many of the genes which can be acquired potentially and pathogens can use them to nullify or diminish the effects of the antibiotics (Dantas *et al.*, 2008; Forsberg *et al.*, 2012; Pawlowski *et al.*, 2016;Berglund *et al.*, 2017;Berglund *et al.*, 2020). So far, all of the approved classes of the antibiotics might they be synthetic, natural, or semi-synthetic in nature have so far met some kind of resistance by their target pathogens. This indicates that there is presence of the resistance factors in the environment for the antibiotics that will never enter the developmental phase unless there is advancement and change in our understanding regarding the design of the antibiotics.

By the passing eons, majority of the ARGs might have evolved slowly from the genes with the other functions (Morar and Wright, 2010;Andersson *et al.*, 2015). The events pertaining to the evolution are mainly caused by the ancestral species transfer events where there was shaping of the overall genetic makeup. Carrying on from immobile chromosomal ARG, a stepwise typical evolution leading to the acquisition of resistance in pathogen. The initial step involves capability of movement of the ARG inside the genome, attained such as via associating with the insertion of the sequences (Partridge *et al.*, 2018; Razavi *et al.*, 2020) or forming gene cassettes as well as incorporating in the integrons (Gillings *et al.*,

2008; Razavi *et al.,* 2017). In the second step the gene is relocated to the element which has the ability to move autonomously among the cells, like a plasmid or a conjugative element.

It is more likely for some of the environments to provide the needed genetic elements which are usually involved in the transfer and mobilization of the ARGs, via presence of the fecal bacteria which are well known for carrying similar elements or might be via environmental conditions where the frequent transfer of the genes is considered favorable (Flach *et al.*, 2017; Shintani *et al.*, 2020). Third step include horizontal transfer of the mobilized gene transfer by having direct pathogen contact or through one of the bacterial hosts that serve as an intermediate. Fourth step might take place at any time of the process is bacterium carrying ARGs is physically transferred to the normal microbiota of the animal or human gut which is an ability defined by the term known as 'ecological connectivity' (Baquero *et al.*, 2019). Higher metabolic activity as well as extensive contact among the cell are factors contributing to increased rate of majority of the steps. All of the said steps such as mobilization by e.g., the insertion sequences (Vandecraen *et al.*, 2017) or the integrons (Depardieu *et al.*, 2007), observes an increase in the abundance of donor cell and subsequently in the opportunities for the transfer as well as horizontal gene transfer (HGT) rate (Scornec *et al.*, 2017;Jutkina *et al.*, 2018), might be increased by the antibiotics. Mainly, even though occurrence of majority of the steps happens when the antibiotics are absent, but the rates are different (Aminov, 2011; Knöppel *et al.*, 2017). Thus, it is important that bottlenecks be studied which play a part in resistance evolution in the pathogen. A likely crucial bottleneck would be that rare genotypes are selected who have resistance which is caused by the mobilization or the HGT or both, otherwise there would be disappearance of the genotypes (Kimura and Ohta, 1969). At all of the stages, mutations for the sake of compensation might occur in the genome of the bacteria which carries the ARG, which in turn lowers the potential costs of the fitness, via causing reduction in the niche overlap or via causing an increase in the competitive capability (Letten *et al.*, 2021). Emergence of the newer ARGs is dependent on the fact that all the events have to align in space and time (Waglechner and Wright, 2017).

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