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THE EMERGING WORLD OF ANTIBIOTICS AND THE TERROR OF ANTIBIOTIC RESISTANT MICROORGANISMS: A REVIEW

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Abstract
In today's time many of the pathogenic bacterial strains have started showing resistance to antibiotics which is one of the biggest health challenges faced. This rising popularity gained by pathogens has a propensity to cause infection in people at any phase of life, in healthcare, veterinary, and cultivation industries, enlisting to primary public health challenges, most countries are going to encounter. Antibiotics used inappropriately in human, animals, food, agricultural arenas have caused a rather catastrophic dilemma. Antibiotic resistance results when the bacteria can resist the action of antibiotics and continue causing infection. Both gram-positive and gram-negative resistant bacteria have been deemed serious and urgent threats as they have evolved to develop resistance mechanisms, as a result, the organisms continue to grow and cause infection, even in the presence of antibiotics. In April 2014, World Health Organization (WHO) published the first global report on surveillance of AMR, illustrates the degree of this antibiotic resistance in various parts of the world and also the existence of large breaks in the prevailing investigation, there fore enumerating to be one of the gravest global public health threats in the world.

Keywords
Antibiotics, antibiotic Resistance, pathogenic bacteria, public health challenge, infection

Introduction

Antibiotics are drugs that are used to destroy or inhibit the growth of bacterial cells. Antibiotics are either bacteriostatic or bactericidal in nature and help the body's immune system to eradicate them[1]. These drugs inhibit the formation of basic genetic material such as the DNA, RNA and hereby inhibiting the protein synthesis too, and this is carried out by many specificactions such as them embrane synthesizing agent.[2] The bactericidal antibiotic is those classes of drugs that kill the bacteria by either interfering with its cell wall synthesis or by inhibiting one of its cell components during replication thus killing it. The bacteriostatic antibiotics are that class that inhibits the further growth of the bacterial infection.

Mechanism of action of drugs

The bacteria are targeted by the antibiotics which prevent them from their cell wall and thereby causing cell death. This is because of the presence of a thick peptidoglycan which is present in most of the bacterial cells. The linear strands of peptidoglycan undergo cross-linking due to transglycosidases, and the peptide chains extend from the sugars present in the polymers, forming the cross-links joining one peptide chain to another.[5] These sugars are specific derivatives of carbohydrates forming the inside layer of the peptidoglycan layer. The sugar components of the layer contain residues of β-(1,4) linked NAM (N-Acetyl Muramic Acid) and NAG (N-AcetylGlucosamine) arranged alternatively [3]. These sugars on either side of the layer are joined together with pentapeptides which are cross-linked by the peptide bond that holds them together and thus strengthening the cell wall. These are the antibiotics whose molecular structure consists of a beta-lactam ring. There are various derivatives of beta lactam antibiotics such aspenicillin (penams), cephalosporins (cephems), monobactams, carbapenems[4] and carbacephems.[5] These are the most widely used antibiotics whose action against the bacterial cell is carried out by inhibiting the cell wall synthesis. Protein Synthesis Inhibitors such as tetracycline, erythromycin, chloramphenicol, and aminoglyco sides are

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the majorly used antibiotics. These antibiotics work as protein-synthesis inhibitors interfering with the cell synthesis and thus inhibiting protein formation. Antibiotics such as erythromycin inhibit the process of protein synthesis by attaching itself to the 23 S ribosomal subunit of the 50 S unit and hence prevents the assembly of the various subunits of 50 S ribosomal unit. Erythromycin, clarithromycin and roxithromycin are the antibiotics that inhibit extension at the transpeptidation stage of synthesis by preventing the 50 Spolypeptide export tunnel.[3]

Replication of all living forms, including bacteria takes place by the replication of the genetic material that is DNA. There is a class of antibiotics that interferes with the replication of DNA by either binding itself to directly one of these or by inhibiting the components of the cell involved in the process of replication and hence the survival. Examples: quinolones, metronidazole, and rifampicin[6]. Quinolones are a primary group of antibiotics that inhibit the process of DNA synthesis by attacking the topoisomerase, the enzyme commonly responsible for the super coiling of the ds DNA strand, most frequently Topoisomerase II. The topoisomerase II is an instrumental enzyme used in the process involved in theme chanism of DNA replication as it cuts the double stranded DNA, relaxes the super coils and then rejoins them together at the cut ends. Therefore, permitting the super coiled strand of DNA to be replicated or even transcribed when they are separate.[7]

Folic acid is a vitamin that is required to make nucleotides and many amino acids. In the absence of an important metabolite like this, the cell would fail to make DNA, RNA and most of the proteins. Bacteria make their own folic acid which is used in many enzymes and many metabolites are formed too. There are certain drugs that inhibit the process of folic acid synthesis that are bacteriostatic because the bacteria cannot reproduce without sufficient folic acid to make DNA, RNA or proteins and broad spectrum as they are effective against various types of bacteria. Different sulpha drugs with the combination of trimethoprim helps ininhibiting different enzymes participating in the mechanism of formation of folic acid. Sulfonamides are competitive inhibitors of dihydrofolatesynthesis. Trimethoprim is responsible for inhibiting the action of the enzyme dihydrofolate reductase. When trimethoprim and this enzyme are used together can be used to cure a wide range of susceptible bacterial infections (gram negative and gram positive).[8]

Antibiotic Resistance: a concern

There has been an increase in antibiotic use over the past years, however, the discovery of the various antibiotics has got slow because of the increased resistance of the pathogens against the existing antibiotics. Due to this, the antibiotic which has got resistant to the pathogen/disease is not able to combat the same. The arising resistance of the various microbes including bacteria, viruses, etc. is due to the mutations in their genome that have caused its evolution. This

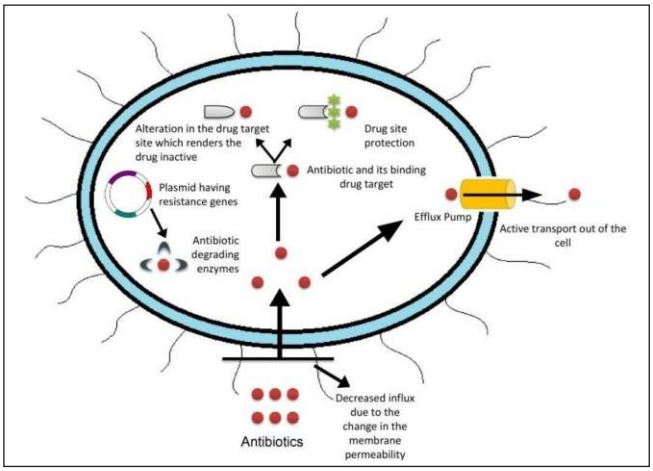

Figure 1: Showing different resistance mechanisms against antibiotics.

resistance renders our drugs ineffective hence threatening the most significant advances in medical history. Antimicrobial resistance is posing a serious global threat to the environment, humans and animals.

Antibiotic Resistant Microorganisms

- Antibiotic resistant *Gonorrhea* strain
- Metronidazole resistant *Clostridium difficile*
- Methicillin resistant *Staphylococcusaureus*
- Vancomycin-resistant *Enterococci* (VRE)
- Extended spectrumbeta-lactamases (ESBL)
- Penicillin resistant *Streptococcus pneumoniae* (PRSP)
- Vancomycin resistant *Staphylococcus aureus* (VRSA)
- Multidrug resistant Tuberculosis (MDR-TB)
- Multidrug resistant *Staphylococcus pneumoniae* (MDRSP)

Antibiotic resistant Gonorrhea strain

Gonorrhea is an infection which is transmitted via sex and spread by the bacteria *Neisseria gonorrhea.* A person is infected with gonorrhea by openings, the bacterial strain entering the body through mouth, anus, penis or vagina. The most common way a woman is infected is by her cervix and the man is mostly infected by the urethra, the tube that carries the urine from the urinary bladder to outside the body.[9]

Mechanism of antibiotic resistance in Gonococcus

Over the past few years, the gonococci bacterial strain has developed tolerance against the action of antibiotic drugs due to the process of mutations and/or gene (whole or parts) acquisition occurring spontaneously, are efficiently chosen because of antibiotic burden in patients and, in the population and generally.[10] On a global scale, this bacteria *N. gonorrhoeae* has shown resistance to almost all significant antimicrobials, including penicillin, quinolones, sulfonamides, macrolides and tetracyclines.[11] This rise of resistance in this bacteria is done by point mutation and also

horizontal gene transfer even with other *Neisseria* species. These resistance mechanisms which have been acquired include the alteration in the drug binding site, increased in activation of antibiotics, decreased concentration of drugs. For example, when there is a mutation in the *penA*gene which is known for encoding the cell wall protein penicillin binding proteins2, confers lesser sensitivity to the beta-lactam drugs [12][13]. The gonococcus strain has known to develop most of the physiological methods of resistance to many antibiotics which are advised during its treatment, e.g., (i) target modification or protection that reduces affinity for the antimicrobials, (ii) modifying or damaging the antimicrobials by enzymatic mechanisms, (iii) increased efflux of antimicrobials, and (iv) decreased influx of antimicrobials. Many genetic determinants responsible for AMR is situated on the chromosomes at the *bla*TEMgene [14][15] and the *tetM*gene[16]. These genes *bla*TEM and *tetM*are responsible for causing high resistance to penicillin and tetracycline correspondingly, and this resistance is suspected to be plasmidborne. Gonococci builds its resistance to antibiotics by the process of transfer of genes (transformation and following recombination in to the genome) or by means of mutations at specific sites. Introduction of antibiotics to gonococcior other *Neisseria* spp. for the treatment of gonorrheal or other infections can pick out for strains which inhibit the mechanism of antibiotics.[12]

Metronidazole resistant *Clostridium difficile*

Clostridium difficile is a Gram positive anaerobe causing *Clostridium difficile* infection (CDI) and disrupting the intestinal environment [17]. The most common way of transmitting CDI is by spores and has the capability of causing severe damage to the colon and can be fatal. There has been an increase in the number of deaths by CDI over the past few years and poses an economic burden as well. [18] According to the data given by Centre of Disease Control (CDC), in United States, this infection is responsible for over 29,000 deaths each year with more than 400000 people getting infected, posing a economic burden of about $1 billion in additional medical budgetary costs.[19] For the first line of treatment, the antibiotics to be used are metronidazole and vancomycin. Most of the CDI's are susceptible to either of the drugs [20]. The other antibiotics used are erythromycin,clindamycin,penicillins,lincomycin,tetracyclines,aminoglycosides,cephalosporins,andfluoroquinolones, which have been used to treat bacterial infections. [21][22] Metronidazole (MTZ)is a nitroaromatic prodrug with a relatively lower molecular weight and can easily diffuse across the membrane of aerobes and anaerobes as well. [23][23] It has developed multi resistance mechanisms which aids in antimicrobial resistance in *Clostridium difficile*. These resistance mechanisms include the mobile genetic elements (MGEs), genes causing rising resistance in bacterial chromosome, modifications concerning the targets of antimicrobials and/or in absorption ways in *C. difficile*, and in the development of biofilm.[19] Different phenomenon such as conjugation, transduction, or transformation of MEG's specifically transposons within different *C. difficile* strains and other bacterialcells help in acquiring antimicrobial resistance. [21]

Amechanismmediatingantibioticresistancein*C.difficile*includesmodificationsintheantimicrobialtargets and/or in the absorption pathways. Data has been suggested that the rising resistance against Vancomyc in might be because of alteration in amino acid constituting the proteins in peptidoglycan biosyn thesis like MurG [24] Some different influences like selective pressure due to exposure to antibiotics in the environment make modifications in the objective sites of antimicrobials and/or in the absorption paths in *C. difficile*. For example, due to this method of selective pressure rifamycin, rifampinandrifaximin classe sofantibiotics, have stopped working against *C.difficile* as they have gained the ability to induce mutations in the sub-unit of the rpoB gene, that translates a RNApolymerase of the bacterial strain[25][26]

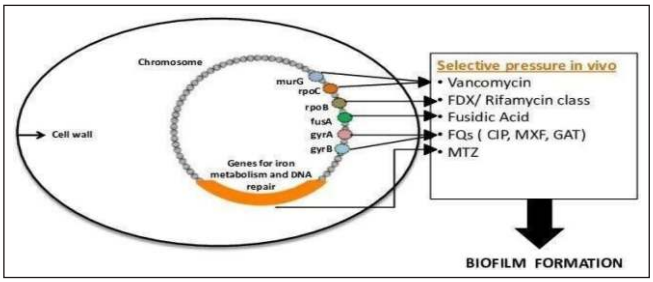

Figure 2: Selective pressure *in vivo* leading to alterations in antibiotic targets and causes antibiotic resistance. The resistance to the antibiotics also stimulates the bio-film formation. Bio-formation viadifferent mechanisms further contributes to antimicrobial resistance in *Clostridium difficile*. *CFs, cephalosporins; CHL, chloramphenicol; CIP, ciprofloxacin; CRO, ceftriaxone; CTT, cefotetan; CTX,cefotaxime; FOX, cefoxitin; FQs, fluoroquinolones; GAT, gatifloxacin; LZD, linezolid; MLSB, macrolide-lincosamide-streptograminB; MTZ, metronidazole; MXF, moxifloxacin; PBPs, penicillin-bindingproteins; TET, tetracycline; VAN, vancomycin.*

Formation of biofilm has been found out to be one of the most important factors contributing to antibiotic resistance. The process involving the formation of biofilm involves a dense multi component matrix of many layers comprising of DNA, proteins, and polysaccharides. [27] It is evident that biofilms have the ability to defend infective bacteria from adverse stresses which may include antimicrobials and hence promote its survival and virulency. [27]

The mechanism of action of Metronidazole is carried out by its reduction by the pyruvate: ferredoxinoxido reductase which is commonly present in facultative anaerobic bacteria, and are responsible for alteration in its chemical structure. Pyruvate: ferredoxinoxido reductase normally triggers the formation of ATP through the process of oxidativede carboxylation of pyruvate. The nitro group in metronidazole while present in the cell acts as an accept or of electrons which

come together and then transfers to the hydrogen ions in the mentioned cycle. The conversion of metronidazole during reduced form is responsible for the creation of a concentration difference that takes up more drugs and stimulates the development of intermediary compounds and free radicals that are lethal to the cell.[23][28][29]

Many studies on the antibiotic resistance in isolates of *C. difficile* from Europe, Asia and North America has reported an increase in resistance to metronidazole as well as to moxifloxacin and clindamycin.[30]

Methicillin resistant *Staphylococcus aureus*

Staphylococcus aureus is a Gram positive bacteria and a usual member of the microbiota of the human body as it is present in the nose of nearly 30% and on the skin of about 20% of the healthy adults. The strength of the ability of aureus to cause infection varies from mild to life threatening. *S. aureus* is known to cause wide range of skin infections and also affects the soft tissues, bones, joints, or it may even cause infection in the prosthetic devices.[31] According to the data taken from the Emerging Infections Program (EIP) MRSA population surveillance(2005–2016) and the Premier and Cerner Electronic Health Record databases (2012–2017) there is an estimated of 119,247 *S. aureus* blood stream diseases, with 19832 connected deaths. Although the number of people getting infections has reduced from 2015, there has been a significant morbidity rate with the number of people catching the infections.[32]

The increased resistance in *S. aureus* is primarily due to increased consumption of antibiotics like methicillin and other beta-lactams. Resistance in MRSA is primarily interceded by *mecA*thatencodes for a penicillin binding protein PBP-2a that is resistant to the mechanism of action by β-lactamsintrinsically[33][34]. When MRSA encounters antibiotics like methicillin, flucloxacillin, dicloxacillin, nafcillinitinactivates the four PBPs present which havea higher-binding-affinity. However, PBP-2a shows a lower binding capacity for methicillin, and then these PBPs, allows the bacterial cell to proliferate in the presence of these antibacterial medicines. PBP 2a is functionally effective in the presence of the different concentrations of β-lactam antibiotics that stops most endogenic PBPenzymes. Then this further takes over for its roles used in the production of cell walls and allows progress in the presence of the β-lactam inhibitors.[35] There are other genes that supervise the phenotype which are methicillin resistant and the PBP-2 a production. MecR1andMecI are genes which are situated up stream of the gene mec A which are responsible for controlling the PBP-2a expression[36]

Vancomycin-resistant Enterococci (VRE)

Enterococcus is a Gram-positive and anaerobic bacteria which is a common part of the intestinal flora. There are nearly more than 17 different strains but *Enterococcus faecium* and *Enterococcus faecalis* are the most common. Overtime enterococcus has developed a resistance mechanism against a strong antibiotic that was used as a first line therapy to treat it in the first place. A characteristic property of the genus *Enterococcus* is that it confirms resistance to a some amount of antibiotic drugs, even though a few varieties (e.g., *E. faecium*) are further vitally resilient than other species [37]. VRE infections are more difficult to treat than other infections with enterococci, because fewer antibiotics can kill the bacteria [38]. In the past few years, enterococcus not only has been resistant to only vancomycin but also to many beta-lactams and also aminoglycosides[39]. This has led to them becoming the new superbugs which are resistant to many antibiotics, making it difficult to find a cure. As recognized in the early1950's, when enterococcus was treated with penicillin, the response rate was lower than expected. Later, it was found that most enter ococciare resistant to activity of β-lactam and glycopeptide antibiotics inhibiting different bacterial strains[40]. Also, several isolates of *E. faecium* are extremely resistant to penicillins, hence their PBP's have low binding affinity for penicillins.[41]

There are different types of Enterococci resistant to vancomycin that have been categorized based on their phenotypes and genotypes, as summarized in the table1. [42]
It was later that vancomycin was proved to be a strong

Table 1: Properties of phenotypes of some enterococci resistant to glycopeptides in many reported isolates.[42][43]

Variable	VanA	VanB	VanC	VanD	VanE
VancomycinMIC (µg/mL)	64->1000	4-1024	2-32	64-256	16
TeicoplaninMIC (µg/mL)	16-512	≤0.5	≤0.5	4-32	0.5
Most frequent Enterococcusspp.	*E.faecium* *E.faecalis*	*E.faecium* *E.faecalis*	*E.gallinarum* *E. casseliflavus*	*E.faecium*	*E.faecium*
Genetic Determinant van	Acluster; acquired	vanB cluster; acquired	vanC1, vanC2 cluster; intrinsic	vanC2cluster;	vanEcluster; acquired
Transferability	Yes	Yes	No	ND	ND

antibiotic and can be used to treat this infection. Vancomycin is an antibiotic of the class glycopeptides that functions when it attaches to the terminal ^{D}-Ala-^{D}-Ala. This terminal molecule is a part of the pentapeptide section of the *N*-acetylglucosamine (NAG)–*N*-acetylmuramic acid (NAM) peptidoglycan (PG) cell wall precursor.[44]

It has been nearly 30 years that vancomycin has been used and without any emergence of marked resistance. [45] However, later resistant isolates were found in England, then in France, followed by Eastern countries of United States.[46] Resistance shown against the glycopeptide antibiotics in *Enterococcus* spp. is controlled by the operon (Van) that is the Vancomycin Resistant operon. The Van operon may possibly be transferred on the plasmid, either chromosomally or extrachromosomally. The Van operon comprises of a response regulator that is *vanS-vanR*;a ^{D}-lactate dehydrogenase gene, *vanH*; a ^{D}-Ala-^{D}-Ala dipeptidase gene, *vanX*; and a type of variable ligase which has 9 variant genes (*vanA*, *vanB*,*vanC*, *vanD*, *vanE*, *vanG*,*vanL*, *vanM*, and *vanN*)[47]

Extended spectrumbeta-lactamases(ESBL)
Beta-lactams are the class of antibiotics which destroy the bacterial cells by acting on their cell wall. It consists of penicillins, carbapenems, monobactams, cephalosporins. The use of betalactam antimicrobials is very common to treat bacterial infections mostly caused by gram negative bacteria worldwide.[48]

The beta-lactams function by inhibiting the final phase in the process for the formation of peptidogly can which is carried out by acylation of the transpeptidase. The acylation of these transpeptidases forms cross-links in the peptides producing the peptidoglycan. PBP's are the objective site to where the beta-lactams bind, furthermore this method of binding thus interferes with the last transpeptidation process which causes failure of sustainability and thus death via process like self-digestion.[49]

The Gram negative bacteria has been exposed to the beta – lactams persistently causing them to develop resistance by forming an enzyme by mutation called as the beta lactamases that renders the antibiotics in active and broadening theirs cope of survival.[50] There has been a surprising rise in the number of beta lactamases and the number has reached 200[51].

The enzymes, beta-lactamases, break down the antibiotic by opening the beta-lactam ring and henceit becomes inactive. The two other enzymes which show a familiar action are of the class plasmid mediated beta-lactamases are TEM-1 and TEM-2. They are present in gram-negative bacteria including Enterobacteriaceae, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*[52]. ESBL is simply transferred among members of *Entero bacteriaceae* because it is plasmid mediated. The distribution of this resistance applies to beta-lactams and also to other frequently utilized antibiotics such as fluoroquinolones, amino glycosides, and sulphonamides.[53]

These enzymes hydrolyze the penicillins and some of the narrow spectrum cephalosporins.

Penicillin resistant *Streptococcus pneumoniae* (PRSP)
There has been an increased resistance in bacteria which has become non susceptible to antibiotics especially penicillin over the past few years. The studies show that there has been a significant rise in the number of penicillin resistant *Streptococcus pneumoniae* in entire Asia as well as the United States. A gradual increase in the intermediate resistance to penicillin (IRP) has been documented in India since 1995. [54][55]

It has been observed that the affinity of the Penicillin Binding Proteins (PBP's) of the gram negative bacteria to bind with the antibiotics have drastically gone down. The isolates were examined from different parts of the world has demonstrated that the decrease in affinity of these PBPs with the antibiotics is resistance mechanism developed by the gram negative bacteria.[56]

The primary resistance mechanism in *Streptococcus pneumoniae* is the alteration in the enzyme targets that are the penicillin-binding proteins (PBPs) for the beta-lactams. There has been observed mutation in the enzyme targets (PBPs) that prove the reduced binding interaction of the beta-lactams to the target sites. However, mutations at points were chosen in the research laboratory, clinical isolates of *Streptococcus pneumoniae* exhibit a structure like mosaic of the altered genes of PBP, the consequence of interspecies gene transfer and events of recombination.[57]

The method of beta-lactam resistance of S. pneumoniae includes genetic mutations that modify penicillin-binding protein structure, following a decreased affinity for all beta-lactam antibiotics.[58]

A study conducted by Reynolds *et al*. showed that, certain to antibiotic-resistant pneumococcal pneumonia, resistance caused 32,398 additional outpatient visits and 19,336 extra hospitalizations. This led to$91 million (4%) indirect medical costs and $233 million (5%) in total costs.[59]

Vancomycin resistant *Staphylococcus aureus* (VRSA)
Vancomycin resistant *Staphylococcus aureus* are the strains of *S. aureus* that have gradually developed resistance against the glycopeptides, especially vancomycin. There were experiments conducted to study about the vancomycin resistant genes and it was observed that *E. faecalis* cantransferits vancomycin resistant genes to*S. aureus* by gene transfer.[60]

Therare VRSA strains that has the transpos on Tn*1546*, which is developed vancomycin-resistant *Enterococcus faecalis*. This bacterial strain has been suspected to modify the structure of cell wall and its metabolic processes.[61]
The newly discovered VRSA from isolates with a vancomycin MIC ≥ 100μg/ml were discovered inwounds of

diabetic patients co-infected by *E. faecalis* and MRSA resistant species. Irrespective of their fundamental variations, the biochemical processes of VISA and VRSA strains has indicated to reveal several shared features.[61]

Vancomycin functions by attaching itself permanently to the terminal ^{D}-alanyl-^{D}-alanine of disaccharide-pentapeptide precursors in cell wall, and thus hindering assembly of the bacterial cellwall. Enterococci has evolved to develop resistance to vancomycin by way of substituting lactate instead of the terminalalanine, that has a significantly decreased affinity for vancomycin.[62]

Many researches of this coagulase-negative staphylococci resistant to vancomycin have demonstrated that these modified cell wall precursors are produced. This is formed, but small quantities as to be included for the degree of resistance detected. [63].

There has been a hypothesis that is yet to be proven, that says these modified cross-links may hinder vancomycin binding to peptides acting as targets.[64]

Multi drug resistant Tuberculosis (MDR-TB)

Multidrug-resistant TB (MDR-TB) is TB that does not act in response to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs. In 2012, there were approximately 450,000 new cases and 170,000 deaths because of MDR-TB.[65]

India has highest burden of Tuberculosis in the world.[66] Figures published by the Ministry of Health in India says that nearly 3 million new cases of TB occur each year in the country.[66]

Tubercle bacilli has a surprisingly high proportion of chromosomal mutation that shows resistance to antibiotics. Latest molecular analysis of some MDRTB strains reckons that the MDR phenotype is a consequence of successive accumulation of individual mutations in distinctgenes, not by novel methods due to single mutagenic events.[67]

The primary explanation for resistance to antibiotics in MTB is the emerging of different mutations in variety of genes encoding for targets to which drug binds or enzymes responsible got activation of drugs. These mutations occur principally in the manner of SNPs, insertions or deletions and to a less significant extent, significant deletions.[68]

The mechanism of antibiotic resistance in TB happens via two mechanisms: (i) resistance which occurs primarily is the transmitted antibiotic resistance takes place when the resistant strains are communicated to a new host, and (ii) the resistance that occurs secondarily or developed resistance to drugs, this happens via gaining of drug resistance mutations to single or supplementary drugs. [69][70].

Multi drug resistant *Staphylococcus Pneumoniae* (MDRSP)

The staphylococcal infections has caused a major concern by showing various antibiotic resistance medication of infections particularly of methicillin-resistant *S. aureus* (MRSA). This has arisen due to the wide spread usage of antimicrobial agents, combined with the spread of an significant percentage of the organism by person-to-person contacts.[71]

Conclusion

This is an undeniable fact that the problem of antibiotic resistance has a severe impact on the global health and the economy of the world altogether. This problem cannot be attained by the combined efforts of the government, the medical professionals and most importantly the public. Before the government talks about the science behind the resistance, it is necessary to create awareness among the public by effective communications, discussions, seminars etc., discussing the harmful effects it has on the society. The concept of properly taking antibiotics and in proper dosage should be inculcated and the harmful effects of resistance to the body should be taught among the people. Apart from the groundwork and interaction with the public, the researchers should take up more research work in the field of AMR, finding the ways with which one can know and develop strategies to combat AMR.

References

1. **Zaman SB in, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N**. A Review on Antibiotic Resistance: Alarm Bells are Ringing. *Cureus* 2017. https://doi.org/10.7759/cureus.1403.
2. **Levy SB, Levy SB**. From Tragedy the Antibiotic Ageis Born. Antibiot. Parad., 1992, p.1–12. https://doi.org/10.1007/978-1-4899-6042-9_1.
3. **Lake P, Drake R.** Structure. Advanced Information and Knowledge Processing. 2014.53–79p.
4. **Holten KB, Onusko EM.** Appropriate prescribing of oralbeta-lactam antibiotics. Vol. 62, A*merican Family Physician*. 2000. p. 611–20.
5. Manual of Clinical Microbiology, 10th Edition. Manual of Clinical Microbiology, 10th Edition. 2011.
6. **Ambrose PG, Owens J, Quintiliani R, Nightingale CH**. New generations of quinolones: With particular attention to Levofloxacin. Vol. 61, Connecticut Medicine. 1997. p. 269–72.
7. **Yoneyama H, Katsumata R.** Antibiotic resistance in bacteria and its future for novel antibiotic development. Vol. 70, *Bioscience, Biotechnology and Biochemistry*. 2006.p. 1060–75.
8. **King DE, Malone R, Lilley SH**. New classification and update on the quinolone antibiotics. *AmFam Physician*. 2000; 61(9): 2741–8.
9. **Rice PA, Shafer WM, Ram S, Jerse A.E.** Neisseria gonorrhoeae: Drug Resistance, Mouse Models and Vaccine Development. *Annu Rev Microbiol*. 2017;71: 665–86.
10. **Unemo M, Shafer WM**. Antibiotic resistance in Neisseria gonorrhoeae: origin, evolution, and lessons

learned for the future. Vol.1230, *Annals of the New York Academy of Sciences*. 2011.

11. **Tien V, Punjabi C, Holubar M.K.** Antimicrobial resistance in sexually transmitted infections. Vol. 27, *Journal of Travel Medicine*. 2020.
12. **Unemo M., Bradshaw C.S., Hocking J.S., de Vries H.J.C., Francis S.C., Mabey D.**, *et al*. Sexually transmitted infections: challenges ahead. Vol.17, *The Lancet Infectious Diseases*. 2017. p.e235–79.
13. **Lewis D.A.** Global resistance of Neisseria gonorrhoeae: When theory becomes reality. Vol. 27, *Current Opinion in Infectious Diseases*. 2014.p. 62–7.
14. **Howell J.T., Wroten J.E.** Penicillinase-producing Neisseria gonorrhoeae in Florida. *J Fla Med Assoc.* 1981; 68(5): 375–6.
15. **Phillips I. & BGR**; Lactamase-producing, Penicillin-resistant gonococcus. *Lancet*. 1976; 308(7987): 656–7.
16. **Morse S.A., Johnson S. R., Biddle J. W., Roberts M. C.** High-level tetracycline resistance in Neisseria gonorrhoeae is result of acquisition of streptococcal tetM determinant. *Antimicrob Agents Chemother*. 1986; 30(5): 664–70.
17. **Ju YC, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM,** *et al*. Decreased diversity of the fecal microbiome in recurrent Clostridium difficile-associated diarrhea. *J Infect Dis*. 2008;197(3):435–8.
18. **Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR**, *et al*. Burden of Clostridium difficile Infection in the United States. *N Engl J Med.* 2015; 372(9):825–34.
19. **Peng Z., Jin D., Kim H.B., Stratton C.W., Wu B., Tang Y.W.,** *et al*. Update on antimicrobial resistance in Clostridium difficile: Resistance mechanisms and antimicrobial susceptibility testing. Vol. 55, *Journal of Clinical Microbiology*. 2017. p.1998–2008.
20. **Peláez T, Cercenado E, Alcalá L, Marín M, Martín-López A, Martínez-Alarcón J**, et al. Metronidazole resistance in Clostridium difficile is heterogeneous. *J Clin Microbiol*. 2008;46(9):3028–32.
21. **Spigaglia P.** Recent advances in the understanding of antibiotic resistance in Clostridium difficile infection. *Ther Adv Infect Dis*. 2016;3(1):23–42.
22. **Johanesen PA, Mackin KE, Hutton ML, Awad MM, Larcombe S, Amy JM**, *et al*. Disruption of the gut microbiome: Clostridium difficile infection and the threat of antibiotic resistance. Vol. 6, *Genes*. 2015.p. 1347–60.
23. **Edwards D.I**. Nitroimidazole drugs-action and resistance mechanisms I. Mechanism of action. Vol. 31, *Journal of Antimicrobial Chemotherapy*.1993. p. 9–20.
24. **Leeds JA, Sachdeva M, Mullin S, Whitney Barnes S, Ruzin A.** In vitro selection, via serial passage, of clostridium difficile mutants with reduced susceptibility to fidaxomicin or vancomycin. *J Antimicrob Chemother*. 2014;69(1):41–4.
25. **Tsutsumi L, Owusu Y, Hurdle J, Sun D.** Progress in the Discovery of Treatments for C. difficile Infection: A Clinical and Medicinal Chemistry Review. *Curr Top Med Chem*. 2014;14(1):152–75.
26. **O'ConnorJ.R., Galang M.A., Sambol S. P., Hecht D.W. Vedantam G., Gerding D.N.**, *et al*. Rifampin and rifaximin resistance in clinical isolates of Clostridium difficile. Antimicrob Agents Chemother. 2008; 52(8): 2813–7.
27. **Dapa T., Leuzzi R., Ng Y.K., Baban S. T., Adamo R., Kuehne S. A.**, et al. Multiple factors modulate bio film formation by the anaerobic pathogen Clostridium difficile. *J Bacteriol*. 2013;195(3):545–55.
28. **Edwards D.I**. Reduction of nitroimidazoles *in vitro* and DNA damage. *Biochem Pharmacol*. 1986; 35(1):53–8.
29. **Müller M.** Reductive activation of nitroimidazoles in anaerobic microorganisms. *Biochem Pharmacol*. 1986; 35(1): 37–41.
30. **Tenover F.C., Tickler I.A., Persing D.H.** Antimicrobial-resistant strains of Clostridium difficile from North America. *Antimicrob Agents Chemother*. 2012;56(6):2929–32.
31. **Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler VG.** Staphylococcus aureusinfections: Epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev.* 2015; 28(3):603–61.
32. **Kourtis A.P., Hatfield K., Baggs J., Mu Y., See I.**, *et al.* Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections—United States. MMWR Morb Mortal WklyRep. 2019;68(9):214–9.
33. **Sharma V.K., Hackbarth C.J., Dickinson T.M., Archer G.L.,** Interaction of native and mutant MecI repressors with sequences that regulate mecA, the gene encoding penicillin binding protein 2a in methicillin-resistant staphylococci. *J. Bacteriol*. 1998;180(8):2160–6.
34. **Fuda CCS, Fisher JF, Mobashery S.** β-Lactam resistance in Staphylococcus aureus: The adaptive resistance of a plastic genome. Vol. 62, *Cellular and Molecular Life Sciences*. 2005.p.2617–33.
35. **Llarrull L.I., Fisher J.F., Mobashery S.** Molecular basis and phenotype of methicillin resistance in Staphylococcus aureus and insights into new β-lactams that meet the challenge. Vol. 53, *Antimicrobial Agents and Chemotherapy*. 2009. p. 4051–63.
36. **Song MD, Wachi M, Doi M, Ishino F, Matsuhashi M.** Evolution of an inducible penicillin-target protein in

methicillin-resistant Staphylococcus aureus by genefusion. *FEBS Lett*. 1987; 221(1):167–71.

37. **Gold H.S.**,**Moellering R.C.**Antimicrobial-Drug Resistance. Vol.335, **New England Journal of Medicine**. 1996. p. 1445–53.
38. **Russo ET, Biggerstaff G, Hoekstra RM, Meyer S, Patel N, Miller B,** *et al*. A recurrent, multistate outbreak of salmonella serotype agona infections associated with dry, unsweetened cereal consumption, United States, 20083. *JFood Prot.* 2013;76(2):227–30.
39. **Cetinkaya Y, Falk P, Mayhall CG**. Vancomycin-resistant enterococci. Vol. 13, *Clinical Microbiology Reviews*. 2000. p. 686–707.
40. **Krogstad D. J., Parquette A. R.** Defective killing of enterococci: A common property of antimicrobial agents acting on the cell wall. *Antimicrob Agents Chemother*. 1980;17(6):965–8.
41. **Grayson M.L., Eliopoulos G.M.,Wennersten C.B.,Ruoff KL.,. DeGirolami P.C., Ferraro M.J.,** *et al*. Increasing resistance to β-lactam antibiotics among clinical isolates of Enterococcus faecium: A 22-year review atone institution. Vol. 35, *Antimicrobial Agents and Chemotherapy*. 1991.p. 2180–4.
42. **Shlaes DM, Etter L, Gutmann L.** Synergistic killing of vancomycin-resistant enterococci of classes A, B, and C by combinations of vancomycin, penicillin, and gentamicin. *Antimicrob Agents Chemother.* 1991;35(4):776–9.
43. **Gold HS.** Vancomycin-resistant enterococci: Mechanisms and clinical observations. *Clin Infect Dis.* 2001;33(2):210–9.
44. **Faron ML, Ledeboer NA, Buchan BW.** Resistance mechanisms, epidemiology, and approaches to screening for vancomycin-resistant Enterococcus in the health care setting. Vol. 54, *Journalof Clinical Microbiology.* 2016. p. 2436–47.
45. **Ingerman MJ, Santoro J.** Vancomycin. A new old agent. Vol. 3, *Infectious disease clinics of North America*. 1989. p.641–51.
46. **Frieden TR, Munsiff SS, Williams G, Faur Y, Kreiswirth B, Low DE,** *et al*. Emergence of vancomycin-resistant enterococci in New York City. Lancet. 1993;342(8863):76–9.
47. **Frieden TR,Munsiff SS, Williams G, Faur Y, Kreiswirth B, Low DE,** et al. Emergence of vancomycin-resistant enter ococci in New York City. *Lancet*.1993;342(8863):76–9.
48. **Walsh CT, Fisher SL, Park IS, Prahalad M, Wu Z.** Bacterial resistance to vancomycin: Fivegenes and one missing hydrogen bond tell the story. Vol. 3, *Chemistry and Biology*.1996. p.21–8.
48. **Shaikh S, Fatima J, Shakil S, Rizvi SMD, Kamal MA.** Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. *Saudi J Biol Sci.* 2015;22(1):90–101.

[49] Eckburg PB, Lister T, Walpole S, Keutzer T, Utley L, *Tomayko J*, et al. Safety, tolerability, pharmacokinetics, and drug interaction potential of SPR741, an intravenous potentiator, after single and multiple ascending doses and when combined with β-lactam antibiotics in healthy subjects. *Antimicrob Agents Chemother*. 2019;63(9).

50. **Awari A, Nighute S, Khatoon M.** Study of Urinary Isolates With Reference To Extended Spectrum Beta Lactamases Detection and Anti biogram. *J Evol Med Dent Sci.* 2013; 2(9): 1049–55.
51. **Rawat D, Nair D.** Extended-spectrum ß-lactamases in gram negative bacteria. *J Glob Infect Dis.* 2010; 2(3):263.
52. **Potron A, Munoz-Price L S, Nordmann P., Cleary T, Poirel L.** Genetic features of CTX-M-15-producing Acinetobacter baumannii from Haiti. *Antimicrob Agents Chemother*. 2011;55(12):5946–8.
53. **Schwaber MJ, Navon-Venezia S, Schwartz D, Carmeli Y.** High levels of antimicrobial coresistance among extended-spectrum-β-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother.* 2005; 49(5):2137–9.
54. **Jayaraman R., Varghese R., Kumar J.L., Neeravi A., Shanmugasundaram D., Ralph R.,** *et al.* Invasive pneumococcal disease in Indian adults: 11 years' experience. *J Microbiol Immunol Infect.* 2019; 52(5):736–42.
55. **Song J.H., Jung S.I., Ko K.S., Kim N.Y., Son J.S., Chang H.H.,** *et al*. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother*. 2004; 48(6):2101–7.
56. **Zighelboim S, Tomasz A.** Penicillin-binding proteins of multiply antibiotic-resistant South African strains of Streptococcus pneumoniae. *Antimicrob Agents Chemother*. 1980;17(3):434–42.
57. **Hakenbeck R, Brückner R, Denapaite D, Maurer P.** Molecular mechanisms of β-lactamresistance in Streptococcus pneumoniae. Vol. 7, Future Microbiology. 2012. p. 395–410.
58. **Jacobs M.R.** Drug-resistant Streptococcus pneumoniae: Rational antibioticchoices. In: *American Journal of Medicine*. 1999.
59. **Reynolds C.A., Finkelstein J.A., Ray G.T., Moore M.R., Huang S.S.** Attributable health careutilization and cost of pneumonia due to drug-resistant streptococcus pneumonia: A cost analysis. *Antimicrob Resist Infect Control*. 2014;3(1).
60. **Weiss A.** Bacterial Toxins: Genetics, Cellular Biology and Practical Applications. Edited by Thomas Proft. *Chem BioChem*. 2013;14(18):2519–2519.

61. **Weiss A.** Bacterial Toxins: Genetics, Cellular Biology and Practical Applications. Edited by Thomas Proft. *Chem Bio Chem*. 2013;14(18):2519–2519.

61. **Gardete S., Tomasz A.** Mechanisms of vancomycin resistancein Staphylococcus aureus. Vol.124, *Journal of Clinical Investigation*. 2014. p. 2836–40.

62. **Bugg TDH, Wright GD, Walsh CT, Dutka-Malen S, Arthur M, Courvalin P.** Molecular Basis for Vancomycin Resistance in Enterococcus faecium BM4147: Biosynthesis of a Depsipeptide Peptidoglycan Precursorby Vancomycin Resistance Proteins Van Hand Van A. *Biochemistry*. 1991; 30(43):10408–15.

63. **Billot-Klein D., Gutmann L., Bryant D., Bell D., Van Heijenoort J., Grewal J.,** *et al*. Peptidoglycan synthesis and structure in Staphylococcus haemolyticus expressing increasing levels of resistance to glycopeptide antibiotics. *J. Bacteriol*. 1996; 178(15): 4696–703.

64. **Srinivasan A, Dick JD, Perl TM.** Vancomycin resistance in Staphylococci. Vol. 15, Clinical Microbiology Reviews. 2002. p. 430–8.

65. **Seung KJ, Keshavjee S, Rich ML**. Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. *Cold Spring Harb Perspect Med.* 2015;5(9).

66. **Nowoslawski A, Krawczynski K, Nazarewicz T, Slusarczyk J.** Immunopathologival aspects of hepatitis type B. *Am J Med Sci.*1975;270(2):229–39.

67. **Singla D, Tewari R, Kumar A, Raghava GPS.** Designing of inhibitors against drug tolerant Mycobacterium tuberculosis (H37Rv). *Chem Cent J.* 2013;7(1).

68. **Gillespie S.H.** Evolution of drug resistance in Mycobacterium tuberculosis: Clinical and molecular perspective. *Antimicrobial Agents and Chemotherapy*. 2002.

69. **Palomino JC, Martin A.** Drug resistance mechanisms in Mycobacterium tuberculosis. Vol. 3, *Antibiotics*. 2014.p. 317–40.

70. **daSilva PEA, Palomino J.C.** Molecular basis and mechanisms of drug resistance in Mycobacteriumtuberculosis: Classical and new drugs. Vol. 66, *Journal of Antimicrobial Chemotherapy*. 2011. p.1417–30.

71. **Okeke IN, Lamikanra A.** Export of antimicrobial drugs by West African travelers. **J Travel Med.** 2003;10(2):133–5.