Antibiotics: mode of action & antibiotic resistance

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ABSTRACT

Antibiotics are the various products of the secondary metabolites in the various microorganisms which show their reaction by inhibiting the growth of various microorganisms which are bacterium. Here we review mode of action of the antibiotics and the history of the antibiotics their discovery the rapid steep and the current scenario of downfall. One of the main points of focus here is the mode of action of various antibiotics which are of mainly five types wherein the drug is involved in various processes like the inhibition of the cell wall synthesis, drugs which attack and inhibit the formation of the cell membrane , various drugs whose target is to inhibit the formation of the nuclear material , inhibition of the formation of proteins by various drugs targeting either of the two subunits of the ribosome there are separate drugs for each subunit and lastly the interference in the cycle of folic acid metabolism.

Another main topic of focus discussed here is that of the antibiotic resistance and the mechanism of how the resistance progresses in our modern world mainly through the livestock. Basically antibiotic resistance can be understood as the ability of the bacterium or microorganisms to stop the progress and working of the various antimicrobials which at some particular point used to work effectively against those microorganisms. The method to have a result for the antibiotic resistance is the process of performing and cumulating the various antibiotic susceptibility tests. Due to various negligent issues like the self-medication, wrong prescriptions, unnecessary issue of antibiotics, overuse in the cattle has led to the global risk of antibiotic resistance in various microorganisms. Various drugs are being developed on the studies which have shown the antibiotic resistance in various new microorganisms.

Keywords: Mechanism, cell wall, Nucleic acid, resistance, β-lactam antibiotics, Sulfonamides

1. INTRODUCTION:

The antibiotics can be understood as the chemical compounds which can be either of the two variants which include them being either bactericidal which means that the chemical compound totally kills the bacteria or the other category which includes the compounds which are the bacteriostatic compounds which include the chemicals which work in a way to stop the growth in microorganisms like bacteria and protozoa.[1]

There are various generations of the antibiotics which fall under the category of beta lactam antibiotic which have their antibiotic activity due to a ring of beta lactam. The beta lactam antibiotics include Penicillins and the cephalosporins.[1]

The first generation of the antibiotics have a very small area of diseases and infections that it can cover, they are effective in the treatment of various ear infections, various diseases like gonorrhea and the syphilis and some of the infections by Staphylococcus bacteria.[1]

The second generation of the antibiotics have a bit large area of application because they can be effective against not only the gram positive but also the gram negative bacteria, they can be useful in treating infections in the ear , various infections in the urinary tract an the respiratory tract.[1]

The third generation of the antibiotics are considered as a part of the broad spectrum antibiotics, they work against both the gram negative and the gram positive bacteria but they have shown more activity against the bacterium lying in the category of gram negative bacteria. They are usually used in the treatment of some severe infections which persist in the respiratory tract, urinary tract.[1]

The fourth and fifth generation of antibiotics are the extended spectrum antibiotics and are only given if there is no other option left.[1]

2. History of Antibiotics:

Not even knowing the exact way of working the substances such as various plant extracts and the molds were used by people from the ancient civilizations from the regions of Iraq, India, Greece, Egypt and China. The remedies for the infections caused by the bacterias have been reported as back as from the 10th century in the Leechbook written by the Bald in the and time of medieval Europe.[12,13].

One of the widely known remedy for the bacterial infection in the eye was a mixture of the wine, bile from the ox and the crushed form of garlic which was then kept in a vessel of brass for nine days as part the procedure. Studying its process by the modern tools this mixture of various bizarre substances actually prove out to be effective against the bacteria *Staphylococcus aureus* when the scientists again had replicated this recipe in the year 2015. [12]. Though there were some such remedies in the past still death from various infections was one of the major setbacks in the history of humans. During the 1800's ,i.e., during the age of industrial development many scientists were looking for the various causes and the infections to prevent the various kind of infections and it was during that time that their focus was on a microorganism which they started to call as bacteria.[12].

A "Germ theory" was proposed by the scientists known as Louis Pasteur and John Tyndall which propagated the idea of that the diseases are caused by the microorganisms and worked on various ways to prevent the substances from contamination. Pasteurization a process in which the liquid is heated to a temperature between the range of 60 to 100° C was invented by Pasteur inn the 1800's, whereas tyndallization a some what similar procedure was invented by Tyndall. In todays world to overcome the antibiotic resistance the process of pasteurization is still used. Difference was that these processes were capable of preventing a food borne problem but they were not capable of curing an ongoing infection in a living being.[14]

Ernest Duchesne who was a French physician changed this mentality and thinking pattern when he observed that the some kind of molds was pivotal in killing the bacteria, so he experimented by treating the pigs who were suffering from typhoid by a microorganism known as *Penicillin glaucum* here he had accidently discovered penicillin but his works went unnoticed. During the first world war where the infections caused a lot of deaths in both the soldiers and the civilians, penicillin was rediscovered under these circumstances by accident by the scientist Alexander Fleming. In the year 1928 while under studying the various of *Staphylococcus* which is a kind of genus of bacteria causing many different kinds or variety of infections.[12]

While growing the petri plates full of *Staphylococcus* Alexander found that out of all his cultures one had a fungus in it then he also noticed that the bacterium he was studying which was the staphylococcus did

not grow in the presence of that fungal mold. He noticed that the fungus there was the *Penicillium notatum* and the substance derived from it was the penicillin the first antibiotic, he later also found out that the penicillin not only worked on the *staphylococcus* but also on many other bacteria which were gram positive in nature. On this discovery of his he published it in the year 1929 but at period of time his work did not receive any relevant attention but even though presented with the difficulty for its wide spread application he continued to work on it and while doing that he also discovered that the *Penicillium notatum* was very difficult to grow and also he had questions as about how long does the effect of antibiotic have inside the body of an infected human being. [12].

Later Alexander Fleming left his work in the early 1930's to the two colleague of his in the oxford university, namely Howard Florey and Ernest Boris Chain, while the world war II was going on these two advanced with much speed on the work related to the penicillin and then they discovered and patented a way for the mass production of the penicillin in the year 1943. This discovery lead to saving lives of thousands of soldiers who would have otherwise died due to various bacterial infections. Once the penicillin was very widely used and known to all another remarkable discovery came up that was of the antibiotic Strptomycin which was derived from the bacteria *Streptomyces griseus* which is found ont the soil this discovery was made by Albert Schaltz and Selman Waksman .from this discovery a major change in the thinking pattern and the style of extracting antibiotics came into play as it proved that not only fungal molds but also the bacteria can be used to produce the antibiotics. Even in the 21st century most modern antibiotics have been found to be derived from the microorganisms found in the soil.[12].

3. Mechanism of Action in Antibiotics

There are two basic methods in which an antibiotic will act against the targeted organisms which are, first is bacteriostatic, and second is bactericidal agent. Bacteriostatic are the chemicals or substances which stop the microbial growth which means keeping the organisms' growth curve in the stationary phase. The other phase in which the organism is actually killed is called as the bactericidal agent, that is the cellular function of the organism are inhibited with the help of a targeted drug reaction with the help of antibiotics and the main targets of the antibiotics are the cell wall synthesis process, cell membrane constituency, nucleic acid disruption protein and the folate synthesis.[2]

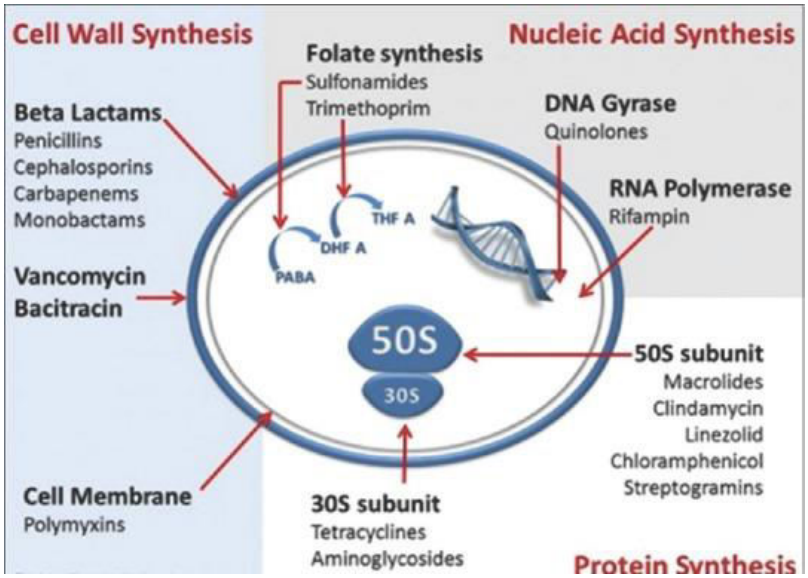

Fig. 1. – Mechanism of action of antibiotics.[25].

3.1Antibiotics targeting cell wall

A substance called as the peptidoglycan is what makes up the cell wall of the bacteria the peptidoglycan is a long sugar polymer transglycosidases. Cross linking of the stands of glycan can be seen under the action of transglycosidases, peptide chain are extending long from the. Under the presence of the PBP which the abbreviated form of penicillin binding proteinglycine redidue get crosslink with D-alanyl-alanine part of the chain of peptide. Cell wall strength is quite improved by this method. [1]

3.1.1 Beta-lactam antibiotics

PBPs are the first or as we can say the primary targets of the β-lactam rings. A portion of the peptide chain called the D-alanyl D-alanine portion which is normally bound by the PBP has been hypothesized to be mimicked by the β-lactam rings. New peptidoglycan cannot be synthesized because the PBP and the β-lactam ring interact are not available for peptidoglycan synthesis which further leads to the disruption of the bacterium.[4]

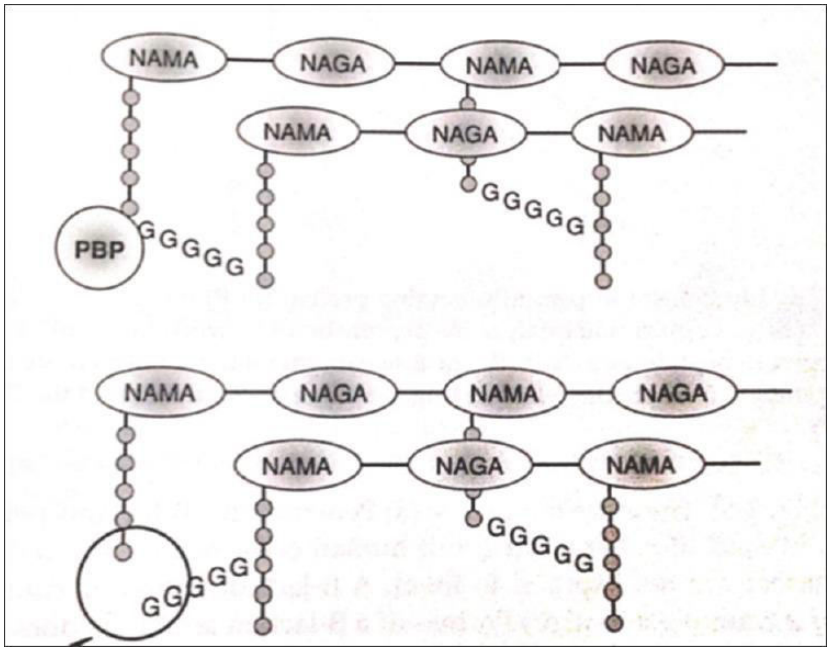

Fig.2- mechanism of action of β-lactam antibiotics.[25].

3.1.2 Glycopeptides

The peptidoglycan subunit precursor of the side chain of the glycopeptides binds with its D-alanyl D-alanine portion. Cell wall synthesis is inhibited because the molecule of the drug known to us as vancomycin stops the process of binding of the PBP and that of the D-alanyl subunit.[4]

3.2. Antibiotics Targeting Cell Membrane

lipopolysaccharide or the phospholipids which form the outer and the inner layers of the cell membrane of bacteria, either one is disrupted by the polymyxins. The ultimate thing is to get the equilibrium wrong and that can be easily fulfilled when the polymyxins get attached to the phospholipids which have the effect of making the cell membrane quite permeable ,hence the cell organelles and other components of the cytosol get leaked and the cell nears its death when the uptake of water increases and the respiration is prohibited eventually.[3]

3.3. Antibiotics Targeting Nucleic Acid Synthesis

3.3.1 Inhibitors of DNA replication

Quinoline

For the introduction of negative supercoils and the resealing of the nicked ends which is done by the bacterial DNA gyrase enzyme, this enzyme is inhibited by the fluoroquinolones. These processes are necessary for the replication or the transcription as the supercoiling which is positive in nature is

necessary. DNA gyrase has found out to have two subunits which are for naming convention known as the A and the B subunit. DNA nicking is done by the subunit A. negative supercoils are introduces by the subunit B henceforth the A subunit works again to introduce then the resealing of the strands. The functions of the resealing and the cutting of the strand in are hampered or interfered when the flouroquinolones are to be binded with the subunit A of the gyrase. After the process of DNA replication in the gram positive bacteria the target for the antibiotic to work is the topoisomerase IV whose function or responsibility is to nick and then separate the daughters DNA. Higher potency against the bacteria which fall under the category of gram positive nature have been proven to be of the higher affinity towards the enzyme. [5,6,7]

3.4. Antibiotics Targeting Protein Synthesis

Inhibitors of protein biosynthesis

To explain this we need to start from the transcription, it is a phenomenon where in the information stored in the bacterial DNA is used to transfer and generate and RNA molecule which is called as the m-RNA or the messenger RNA. After that comes the next step wherein the cell organelle called as the ribosome helps by the processing and production of the proteins by the process called as the translation where in information is translated from the m-RNA. As a catalyst to the process of biosynthesis of proteins the ribosome and the other cytoplasmic factors play their role. [8,9].

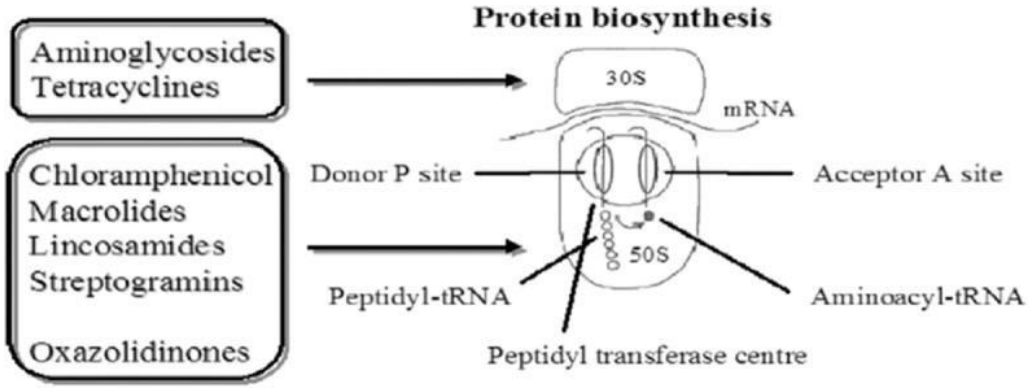

Fig.3.- Site of action of protein biosynthesis inhibitors[25].

3.4.1 Inhibitors of 30S subunit

Aminoglycosides(AG):

The outer membrane of the bacteria are negatively charged and the Aminoglycosides whose molecules are positive and thus it leads to the formation of some large pores which helps the medication in the form of the antibiotics to enter inside the bacterium. The energy created in the bacterium takes place with the help of an electron motive force and the oxygen and this whole process take place in the cell membrane of the bacteria in inner fold like structures called the mesosomes, and the energy required thus to pass the

antibiotics through the membrane is generated. As anaerobic bacteria do not ned oxygen and do not survive in oxygen rich environment thus no proton motive force and thus no energy to transfer the molecules of antibiotics hence the amino glycosides do not work against the anaerobic bacteria. The AG gets synergized and the antibiotics which thus further stop in the cell wall synthesis. Which are like the β-lactam or the glycopeptides because of the beneficial reason which is that the penetration rate and power of the glycopeptides inside of the cell at quite low doses. In the 30S unit of the bacterial ribosome the aminoglycosides react with the 16S r-RNA, they cause the premature terminating of the mRNA by causing the misreading.

Tetracyclines :

To prevent the process of binding of the t-RNA at the A site in the 16S – r-RNA sequence of the 30S sub unit of the ribosome there are various antibiotics under the category of the tetracyclines specifically the tetracycline, minocycline, chloroeertacycline or the doxycycline.[5,7]

3.4.2 Inhibitors of 50S subunit

Chloramphenicol :

In the 50S sub unit of the ribosome at the 23S r-RNA site, the chloramphenicol. Reacts with the very conserved units of the peptidyl transferase present there. Therefore it then enables the inhibition of synthesis of protein by not letting the t-RNA bind to the site of the A site of ribosome.[5,8]

Macrolides:

Translocation which is an early stage of the protein synthesis comes under affect when the macrolides are administered in the body the aim of these antibiotics is to target the 50s subunit of bacterial ribosme which has peptidyl transferase center in the 23S r – RNA. As a result the peptide chains are not allowed to get matured and thus get detached prematurely. Similar kind of action mechanism is shown by lincosamides , macrolides and the streptogramins B.[5,7]

Oxazolidinones:

This category contains a totally synthetic antibiotic which is known by the name of Linezolid and has been approved in the recent past. There are many stages wherein the oxazolidinones can disturb with the protein synthesis which are those of :

First, they get binded to the 23S r – RNA which is present in the 50S subunit and thus stop the synthesis of protein. Second way is they lower the inhibitoy effect of the 70S subunit and react with the peptidyl – t – RNA [11, 12].

3.5. Antibiotics Targeting Folic Acid Metabolism

Folic acid metabolism inhibitors:

Sulfonamides and trimethoprim

There are many different steps in the folic acid cycle and to inhibit them trimethoprim and the sulphonamides are used. When the combination of these two drugs at various ratios are administered at various steps of the biosynthetic pathway they have seen to show synergy and the rate of getting resistant by the mutation gets quite low. [5]. Sulfonamides show a greater affinity towards the enzyme for p – amino benzoic acid which is the natural substrate and thus it stops the dihydropteroate synthase in competition. Inhibition of the dihydrofolate reductase enzyme is done in the later stages by the trimethoprim. [5]

4. Antibacterial Drug Resistance

The capability of the various microorganisms to have a resistance against the activity of the drugs which come under the category of antimicrobials which were often used to get the microorganisms out of the system this is the definition of antibiotic resistance. When the threshold of antibiotic over use and specially the antibacterial drugs misuse is done such that the usual or the conventional methods of doses and treatment are not useful against the microorganisms which have become resistant. If a person is administered to the very less dose of an antibiotic or if the person does not completes their full course of medication and leaves it incomplete then the process of negligence will eventually lead to a high level resistance against the antibiotics which is a slow process and once the body has developed its resistance against the antibiotics the dosage which would have been previously sufficient to fight a particular strain or a wide spectrum of bacterias will not prove to sufficient and useful once resistance has developed.

4.1 History of Antibiotic Resistance

Currently the numbers of antibiotics available are all divided among the twelve classes which in total have over a hundred different antibiotics. Generally the division of the antibiotics can be made by the process in which they can act against or in other words remove the infection. The various methods can include the processes to stop the synthesis of the cell wall, stopping the synthesis of the nucleic acids at various steps, stopping the various pathways which are metabolically related to the growth and division of the bacteria, various processes that can lead to the changes and thus disintegration of the cell membrane

and the various methods to stop the protein Antibiotic resistance. In the year 1968 a new disease commonly known as the MRSA was identifies its full form is Methicillin – resistant *Staphylococcus aureus* which was recorded in the United States of America.[16]

In the year 1972 an antibiotic named as the vancomycin was reportedly showing effective measures against the MRSA and thus was employed in treating for the disease. For over a decade this method of treatment was taken in the regular use for anybody who turned up with it but in the year 1983 the first case of vancomycin was reported. It plotted a pattern where in it seemed as if it was like a race to invent a new drug then with its extensive use the bacteria develop the resistance over a decade. The bacteria of various kinds have almost developed the resistance against the antibiotics of almost all kind from the time the first reported case of MRSA has been found.[16,17]

Another widely reported case of the antibiotic resistance is that of the disease known as the CRE which is the abbreviated version of the Carbapenem – resistant Enterobacteriaceae. The family to which the *Klebsiella* and the very popular *Escherichia coli* also belong, it is a very large family of gram negative bacteria and the name of the family is Enterobacteriaceae. One of the few families of bacteria found in the guts of human beings is the family Enterobacteriaceae. As in a survey done during the early 1990's mostly in the year 1992 in the United States of America, it claimed that the infections relating to have a link with the CRE were quite less. Since then the reported number of cases relating to the resistance have risen considerably and in the year 2013 another surey done by an American agency (CDC) showed that in a single year there were approximately a little over nine thousand recorded cases of the infections of CRE and themore horrifying numbers were those of the deaths where in a single year about 600 people even died because of the developed resistance in the bacteria. Since then the CRE had been given the name of the "superbug" by the same agency, CDC.[15]

4.2 Mechanism of bacterial resistance

Resistance to bacteria can happen because of two mechanisms: the acquisition of resistance and the other mechanism is the acquired resistance. The first kind of resistance which is the acquired resistance it happens when over the time there are some permanent changes or we can say the altercations in the molecule of the DNA which helps the bacteria internally to get a resistance against an antibiotics mode of action. Whereas the other kind of resistance adopted by the bacterium is the acquisition of resistance it is a little complex method wherein the bacteria move out and transfer the nuclear or the genetic material and

information to another bacteria by doing that they do not get perished and thus getting a resistance permanently.[18].

4.2.1 Acquired resistance:

There are various effects by which the bacteria can have the acquired resistance towards the antibiotics. One way can be when the evolution of a particular bacteria takes place in a way that it can fight off the various effects after being administered to an antibiotic by secreting an enzyme which is responsible for deactivating the drug molecules. It can work by getting the target to alter itself, or may be working and changing its metabolism in a particular way such that the uptake of antibiotics in the bacterial cell and gets reduced so much that it doesn't kill the bacteria and the last way is in which the process of outward pumps or efflux pumps help more in the elimination than usual. [16,18]

Bacteria gets deactivated when it comes under the influence of the Penicillin where the drug modulated the procedure of cell wall formation in bacteria and hence bacteria gets inactivated. An enzyme known as the beta – lactamase is secreted by the bacterium which has developed resistance molecular structure of the Antibiotic resistance can thus be broken down by these particular beta – lactam enzymes which thus work in deactivating the properties labeled as antibacterials. An example of the acquired resistance is the bacterium *Pseudomonas aeruginosa* which has undergone such mutations that have ultimately lead to decrease in the permeability of its cell wall to the antibiotics, *Pseudomonas aeruginosa* is a gram negative bacteria. [16,18].

4.2.2 Acquisition of resistance:

By a technique known as the plasma transfer the bacteria can move its nuclear or the genetic materials to other bacteria and another possibility is that they can mutate at that very moment spontaneously. The genes relating to the antibiotic resistance against various antibiotics are present in an organelle called as the plasmid which can be expressed as additional DNA as it constitutes of the various small pieces of DNA. A single plasmid in a bacterium can contain various types of genes or mutations for resistance against many antibiotics. Various bacterias can usually exchange the plasmids with each other and hence different kinds of bacterias can also have resistance for that particular antibiotic. An example for the above explanation is the case where klebsiella and the Escherichia coli transfer their plasmids and nuckear material with each other and thus both of them have the resistance against the wide spectrum beta lactam antibiotics. [16,18].

4.3 How Antibiotic Resistance Spreads:

Antibiotic resistance in various bacterias can develop due to various different reasons there are usually four reasons why that happens, they are stated as follows:

1. Proper committee and regulatory laws to oversee the usage is absent.
2. To keep the cattle and livestock healthy the rearers have been injecting them with more amount than needed and that also on a regular basis.
3. In humans also the overuse and illegal and inappropriate antibiotic intake and prescription.
4. Lack of new and innovative ways to deal with the infections so same treatment over the decades.

(1) Overuse and inappropriate prescribing.

In the history of the human medication the medicine which has been most easily and commonly prescribed to an individual are the antibiotics. Doctors have been prescribing the medicine even where they are not needed and sometimes the inappropriate prescriptions can damage the patients. For example let's see a case where a person goes to a doctor and tells that he had a sinus infection but the doctor did not test it the infection had a bacterial origin or it had a viral origin, if the infection had a viral origin then the person took antibiotics for no reason. According to a research almost fifty percent of the antibiotics prescribed in the United States of America are unnecessary. A different problem that is usually countered by the patients who are on a medication of antibiotics which has a period of a long time in some of the cases due to the evolutionary point of view the bacteria gets under the pressure to survive and then it mutates. In a healthy human beings body the number of healthy bacteria is in billions. The bacteria which are resistant and have evolved get an edge when the whole flora of the gut is bombarded with broad spectrum antibiotics majority of the bacteria get killed off.[18,19].

(2)Extensive use in livestock.

As in a report from the year 2017 the number of animals in the country as far more than the human beings. The antibiotic resistance has a progress pattern in which chain of the resistance fairly progresses.

This progress or the chain has been on an average done in the six steps first one is when the animals that are reared or in other words the livestock are subjected to regular doses of the antibiotics then comes the, second step wherein we can call it as the incubation period where the bacteria present in the digestive tract of the animal mainly in the gut region gets mutated and the new strain of the resistant bacteria gets developed. [20].

The third step is where the bacteria moves out of the gut region into the outer environment and that can happen through the feces which are in contact with the crops consumed by the humans that also in two forms either direct contact or in the form of fertilizers and the other way is wherein the antibiotic resistant bacteria is on the meat consumed directly and uncooked. Fourth step is when these fertilizers are used in the fields and the fifth step is the step where the antibiotic resistant bacteria enters the human body through the crops or the meat. The last step is where the bacteria incubating in the guts of the humans and thus spreading from there. Back in the year 1976 various researches taking place at the University of Tufts showed the relations between the constant use of antibiotics on the cattle and various other farms and the progression of the antibiotic resistant bacteria in the modern human population. [20].

(3) Lack of new therapies.

Since the year 1983 there has been a downward slope in the field of new antibiotics coming up every year in the market with a constant downfall. The WHO which is the World Health Organization released a report in the year 2017 that the number of antibiotics which are under the development phase in the labs are very less and that this deficiency is very severe in relation to consequences with the humanity. [21]. In their report they also mentioned that most of the drugs on which work is been done are just the modification of the drugs which already exist new drugs with same components just with stronger doses in some cases. [21].

(4) Regulatory.

All the hospitals are to have required an antimicrobial stewardship program but less than thirty percent have them. This program is considered important because they are necessary for the maintenance and steady progress of various programs pertaining to the improvement in quality in hospitals. [22]. Programs like these are also very important because they perform the pivotal role in the overseeing and stopping the unnecessary use of antibiotics and thus further in the longer run reducing the adverse side effects of the various antibiotics.[22].

5. FUTURE PROSPECTS

There are studies going on which have shown that in the environment of the hospital the bacteria have developed resistance against the various chemicals that are in use to disinfect the hospital floor, slabs and various other places and have also turned out to be resistant against the hand sanitizers which are alcohol based. This is a major issue in today's time because the hand sanitizers that is the alcohol rubs are the ever ready on the go method of getting ones hands disinfected but if the bacteria have develop resistance against the then it means the bacteria will travel to many rooms of the healthcare environment by the workers hands.[23,24]

The fact of ineffectiveness of the alcohol based hand sanitizers does not indicates that one should stop their use completely but in addition to it the frequent use of the habit of washing the hands with soap and water very vigorously proves to be an effective method of fighting against the bacteria. These days one of the most urgent needs in today's world in the related field of public health is to find a cure for the various deadly infections which have been reported to be caused by an yeast like fungus which is multidrug antibiotic resistant whose name is *Candida auris*. It has shown to develop drug resistant at a very fast rate and has been found on the surfaces which have been cleaned with the disinfectants and has shown its capability to thrive in the hospital environment. This can be a very important area of drug development.[23,24].

6. CONCLUSION

The antibiotics can be understood as the chemical compounds which can be either of the two variants which include them being either bactericidal, the other category which includes the compounds which are the bacteriostatic compounds.

There are various ways in which the antibiotics act against the bacterium which are, the cellular function of the organism are inhibited with the help of a targeted drug reaction with the help of antibiotics and the main targets of the antibiotics are the cell wall synthesis process, cell membrane constituency, nucleic acid disruption protein and the folate synthesis. The capability of the various microorganisms to have a resistance against the activity of the drugs which come under the category of antimicrobials which were

often used to get the microorganisms out of the system this is the definition of antibiotic resistance, the resistance obtained is of two types: Acquired and acquisition of resistance. The various ways which are the reason for the resistance in a bacterium are the Overuse and inappropriate prescribing, extensive use in livestock, lack of new therapies, regulatory issues.

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