Bacterial Resistance Against Antibiotics

Anil Kumar and Nikita Chordia

Abstract From the time when discovery of penicillin was done in 1928, antibiotics are considered to be critical for public health that save the lives of millions of people around the world. Antibiotics are considered to be bactericidal which means capable of killing the bacteria. Some people call them as bacteriostatic which cease bacterial multiplication. These act without killing or damaging the body of the person. In recent years, it has been observed that more and more bacteria are becoming resistant to most of the frequently prescribed antibiotics. This situation is getting alarming day by day, and cure for even common diseases is becoming more expensive. Bacteria develop resistance to adapt their environments and ensure their survival. Drug/antibiotic resistance can be innate or acquired; there are many ways to acquire the resistance. It is becoming difficult to effectively treat wide variety of infections due to multidrug resistance. To control the drug resistance, misuse of antibiotics should be stopped, and regulations must be followed. In addition to control of drug resistance, it can be overcome by using additional molecules with antibiotics. Bacteria are finally overrunning our way of defense, so there is an urgent necessity to discover more antibiotics to combat the bacterial infections. To speed up the research, there is a need to advance the microbial informatics, particularly the development of databases and tools. Bioinformatics is the hope to help in easy availability of the information regarding resistance genes, associated proteins, available literature, cluster of orthologs (COG), pathways, and all other information concerning antibiotics.

1 Introduction

We all are exposed to the tiny microbes including bacteria, viruses, fungi, and protozoan. Some of them cause infection and are called pathogens, and others are even harmless inhabitants of our body. Human body has natural defense system against these pathogens, but sometimes it fails to control the infection. This leads to the development of the antibiotics (also called antimicrobials) which interfere with

A. Kumar (✉) • N. Chordia
School of Biotechnology, Devi Ahilya University, Khandwa Rd., Indore 452001, India
e-mail: ak_sbt@yahoo.com

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the specific life processes of the organism. These are the medicines that kill pathogens without harming humans. These include both synthetic and semisynthetic antibiotics (Davison et al. 2000). Antibiotics are unique therapeutic agents that are directed to invade organism. They block the key reaction(s) in the pathogenic bacteria causing its death and/or inhibiting its multiplication. These are the drugs which can be taken orally, intravenously, or intramuscularly resulting in counter of the infection. This helps the immune system to fight against the infection. However, sometimes, excess use of antibiotics in an individual may affect the microbial ecology of the host (Monroe and Polk 2000). No single antibiotic is effective against all pathogenic bacteria. The antibiotics, viz., gentamicin and amoxicillin, which affect diverse variety of bacteria have been named as broad-spectrum antibiotics, whereas the antibiotics like vancomycin and penicillin which affect selective bacteria have been named as narrow-spectrum antibiotics (Heinemann 1999).

Since the introduction of penicillin in 1940s, more than hundreds of antibiotics have been discovered. Penicillin was hailed as a "miracle drug," and future was predicted as free of infectious diseases (Bentley 2005). The antibiotics are classified based on the spectrum as broad or narrow, similarly based on the route of administration as injectable or oral, and on the type of activity as bactericidal or bacteriostatic. Besides, antibiotics have also been named as β-lactam, macrolides, tetracyclines, fluoroquinolones, sulfonamides, aminoglycosides, imidazoles, peptides, and lincosamides on the basis of structural aspects. Structurally homologous antibiotics exhibit similar antibacterial activity (Kohanski et al. 2010; Wong et al. 2012).

Bacterial resistance can be of two types, viz., intrinsic or innate and acquired resistance. Innate resistance relies on the physiology and biochemistry of the bacteria and is considered to be peculiar property of specific bacteria. However, acquired resistance in a bacteria is developed by different means like transformation of specific gene(s) using bacterial and/or phage vectors, jumping genes, integrons, and site-directed mutagenesis in bacterial gene(s) itself or by a combination of these (Giedraitienė et al. 2011). A list of few resistant bacteria and names of the antibiotics for which bacteria is resistant is given in Table 1.

The frequent prescription of antibiotics by the doctors and habit of taking antibiotics without consulting the doctor especially in the developing countries are considered to be the main causes of resistance in bacteria against a particular antibiotic or a combination of antibiotics. In many cases, it has been observed that initially a particular bacteria remains sensitive to an antibiotic; however, it adapts slowly and ultimately becomes resistant to it. Many times, doctors change the prescription with different antibiotics which may lead in acquiring resistance against one or more drugs, and the condition is called as multidrug resistance (MDR) (Giedraitienė et al. 2011). Nowadays, many multidrug-resistant bacteria are known and to mention a few are specific strains of *Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

In many bacteria, mode of adaptation for antibiotic resistance has been elucidated which include drug-inactivating enzyme, drug removal from the cell,

Table 1 Bacteria and their resistance to antibiotics

Bacteria	Resistant to antibiotics	References
Acinetobacter baumanii	Imipenem, meropenem, antipseudomonal agents, fluoroquinolones, carbapenems	Lee et al. (2012)
Clostridium difficile	Fluoroquinolone antibiotics, such as ciprofloxacin and levofloxacin	Loo et al. (2005)
Enterococcus faecium/ vancomycin resistant-enterococci (VRE)	Vancomycin, streptomycin, gentamicin, penicillin, ampicillin	Landman and Quale (1997), Arias et al. (2010)
Escherichia coli (ESBL strain)	Oral cephalosporins, TMP/SMX, fluoroquinolones	Prakash et al. (2009)
Klebsiella pneumoniae-extended spectrum beta-lactamases (ESBL)	Second-, third-generation cephalosporins, aztreonam, carbapenem	Paterson et al. (2004), Woodford et al. (2004)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	β-Lactam ringed, viz., ampicillin, amoxicillin, penicillin	Liu et al. (2011)
Multidrug resistant *Mycobacterium tuberculosis* (MDR-TB)	Isoniazid, rifampin, possibly streptomycin	Keshavjee and Farmer (2012)
Mycobacterium tuberculosis	Isoniazid, rifampin	Gillespie (2002)
Neisseria gonorrhoeae	Penicillins, tetracyclines, fluoroquinolones, macrolides, cephalosporins	Farhi et al. (2009)
Pseudomonas aeruginosa	Cephalosporin, cefepime, tobramycin, gentamicin	Lister et al. (2009)
Pseudomonas aeruginosa (multidrug-resistant strains)	Resistance against combination of more than one antibiotics, viz., meropenem, cephalosporins, etc.	Mesaros et al. (2007)
Salmonella enteric	Ampicillin, chloramphenicol, tetracycline, sulfamethoxazole, trimethoprim, fluoroquinolones	Quinn et al. (2006)
Staphylococcus aureus	β-Lactam, fluoroquinolones, gentamicin	Chambers and DeLeo (2009)
Staphylococcus aureus (cMRSA strain)	β-Lactam ringed antibiotics, cephalosporins, erythromycin	Liu et al. (2011)
Staphylococcus aureus (partially resistant to vancomycin, VISA)	Vancomycin, β-lactam ringed antibiotics	Weinstein (2001), Fridkin (2001)
Staphylococcus epidermidis (methicillin resistant)	Penicillin, amoxicillin	Uçkay et al. (2009), Fey and Olson (2010)
Streptococcus pneumoniae (multidrug resistant)	Resistance against combination of more than one antibiotics, viz., penicillin, erythromycin, doxycycline, etc.	Mandell et al. (2007)

acquisition of a target, modification in current target, and reducing cell permeability. Still, critical new aspects of drug-resistance mechanism are continued to be discovered (Livermore 2003).

There is more treatment cost, longer stay as indoor hospital patient, chances of getting more infections, and more chance of death if a person is infected by drug-resistant bacteria (Heymann 2006). Therefore, scientists have realized to discover other ways of treatments such as specific vaccines for common bacterial infection. Unfortunately, in spite of much requirement of new antibiotic therapies, not so many new drugs/antibiotics have been approved by the controlling agencies like FDA. Therefore, there is really a difficult situation due to bacterial resistance against antibiotics.

Now, we have entered in the "post-antibiotic" era as choice for antibiotic is declining (Gandra et al. 2014). The present situation arose due to frequent and not judicious prescription of antibiotics to the patients and manufacturing of the same by the industries. It is considered that antibiotic resistance and multidrug resistance developed in pathogenic bacteria due to underuse and overuse of antibiotics. Besides, the misuse of antibiotics, inadequate diagnostics, and use of antibiotics in farming, aquaculture, and poultry contribute in resistance.

To treat the pathogens which are resistant to available treatment, new antibiotics must be discovered. However, there is a need of new antibiotic, but the number of newly approved drugs is continuously declining since new drugs are being produced either from natural compounds or by chemical modification of existing drugs (Donadio et al. 2010). Many tools and databases are available that contain information about resistant bacteria genome, drug-resistant genes, COG, annotation, and many more. These databases will help in fast discovery of new compounds that can treat the resistant microbes.

2 Mode of Action of Antibiotics

The different antibiotics work by inhibiting different bacterial cellular processes. The main bacterial cellular processes which are inhibited by the different antibiotics are biosynthesis of cell wall, polypeptide (protein), DNA, RNA, metabolic pathways, cell membrane, etc. (Sefton 2002; Kohanski et al. 2010; Wong et al. 2012).

2.1 Cell Wall Biosynthesis Inhibitors

It has been found that many antibiotics work by inhibiting the biosynthesis of cell wall (Tomasz and Waks 1975). The antibiotics commonly target bacterial cell wall formation because animal cells do not have cell walls. Bacterial growth is prevented by inhibiting peptidoglycan synthesis which is an important part of cell wall. This is particularly important when bacteria are dividing, because it is needed for the new cell that is forming. As the bacterium starts to replicate, it first elongates to about twice its normal size. So, more peptidoglycan is made for the extra surface area. But when these antibiotics are present, the peptidoglycan cannot cross-link properly, so

Table 2 Cell wall biosynthesis inhibitory antibiotics

Antibiotic class	Name	Primary target
β-Lactam	Penicillins, carbenicillin, ampicillin, penicillin G, cloxacillin, cephalosporins, monobactams	Penicillin-binding proteins
Glycopeptides	Vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, and decaplanin	Terminal dipeptide having alanyl moieties
Others	Alafosfalin	Terminal dipeptide having alanyl moieties
	Bacitracid	Prenylation
	Seromycin	Alr and Ddl enzyme
	Monurol/monuril	MurA enzyme
	Tunicamycin	Conversion of the undecaprenyl phosphate to the lipid I intermediate

the cell wall is very weak in places. These bacteria are subjected to osmotic lysis and subsequently die. It means that all of these antibiotics that inhibit peptidoglycan synthesis are bactericidal because they directly kill bacteria (Fisher et al. 2005).

It is found that β-lactam ringed antibiotics generally inhibit biosynthesis of bacterial cell wall. The examples are penicillins, carbenicillin, ampicillin, cloxacillin, cephalosporin, etc. The other classes of cell wall biosynthesis inhibitors are glycopeptides. The examples are bleomycin, vancomycin, decaplanin, etc. These glycopeptides are mono- or polycyclic peptides synthesized without involvement of ribosomes and have bound carbohydrate (glycol) moiety in them. They do this by binding with amino acids within the cell wall that prevents the addition of new units to the peptidoglycan (Silver 2003). Table 2 shows the classes of antibiotics, names, and their primary targets which inhibit cell wall biosynthesis.

2.2 Nucleic Acid Biosynthesis Inhibitors

Antibiotics can target nucleic acid (either RNA or DNA) synthesis. Nucleic acids are very important for a cell as these are the instruction manuals of the cells. When a cell divides, it must first replicate its DNA to give the new cell. Therefore, inhibiting nucleic acid synthesis is a good strategy to hinder bacterial growth (Goldberg 1965). The enzymes that carry out DNA and RNA syntheses are different enough between eukaryotic and prokaryotic cells. So there is selective toxicity. Prokaryotic replication and transcription processes include three steps: initiation, elongation, and termination. Antibiotic drugs have been developed to target each of these steps. For example, the antibiotic rifampin inhibits initiation process in RNA biosynthesis by binding with DNA-dependent RNA polymerase which is involved in the biosynthesis of RNA using DNA as a template. The antibiotic molecule is

Table 3 Nucleic acid synthesis inhibitory antibiotics

Antibiotic class	Name	Primary target
Rifamycins	Rifapentine, rifalazil	RNA polymerase (EC 2.7.7.6)
Resistomycins	Resistomycin, resistoflavin	RNA polymerase
Fluoroquinolones	Gemifloxacin, levofloxacin, ofloxacin, moxifloxacin	DNA gyrase
Sulfonamides	Sulfafurazole, sulfacetamide, sulfisomidine	Dihydropteroate synthase
Others	Novobiocin	DNA gyrase

thought to bind to the polymerase in such a way that it creates a wall that prevents the chain of RNA from elongating. In the presence of rifampin, bacteria cannot transcribe any gene that they need to carry out their normal functions, and therefore they die (Boehme et al. 2010).

Another example is quinolones that inhibit DNA synthesis by interfering with the coiling of DNA strands (Khodursky et al. 1995). During DNA replication, DNA gyrase relieves the torsional stress. As the replication fork moves along the bacterial chromosome, the strand of the DNA becomes supercoiled or excessively twisted. DNA gyrase binds to the DNA and cuts one of the strands to untwist before resealing. However, when quinolones are present, DNA gyrase gets inhibited and cannot reseal the strand. This causes the bacterium chromosome to break into smaller fragments and kills bacteria. Table 3 shows the classes of antibiotics, names, and their primary target which inhibit nucleic acid biosynthesis.

2.3 Protein Biosynthesis Inhibitors

Many antibiotics inhibit the synthesis of new proteins resulting in inhibition of cell growth/proliferation (Mukhtar and Wright 2005). Antibiotics inhibit bacterial protein synthesis at the ribosomal level and not eukaryotic protein synthesis due to the difference in the prokaryotic and eukaryotic ribosomal structures. The bacterial and eukaryotic ribosomal subunits have differences in RNA to protein ratio, size, sequence, etc. Due to these distinctions, antibiotics destroy microbes by targeting bacterial ribosomal subunits; however, eukaryotic ribosomal subunits are not targeted. Antibiotics work at different levels of translation for inhibiting protein synthesis like initiation, elongation, and termination. For example, tetracyclines bind to the 30S ribosomal subunit at the A site and prevent the attachment of aminoacyl-tRNAs. This hinders the next polypeptide string to be brought onto the ribosome (Brodersen et al. 2000). Another antibiotic, chloramphenicol, interacts with the larger (50S) ribosomal subunit and prevents peptide bond formation. When chloramphenicol is around, the amino acid cannot be linked together into a polypeptide string (Wolfe and Hahn 1965). Table 4 shows the classes of antibiotics, names, and their primary target which inhibit protein biosynthesis.

Table 4 List of antibiotics that inhibit protein biosynthesis

Antibiotic class	Name	Primary target
Tetracyclines	Oxytetracycline, doxycycline, tetracycline, demeclocycline, minocycline	Smaller (30S) ribosomal subunit and subsequently, prevention of binding of aminoacyl-tRNA onto the ribosome
Aminoglycoside	Tobramycin, gentamicin, amikacin, streptomycin, spectinomycin	Smaller (30S) ribosomal subunit and subsequently wrong amino acid incorporation due to misreading
Macrolides	Fidaxomicin, telithromycin, kitasamycin	Larger (50S) ribosomal subunit, interfere in chain elongation by interfering in addition of peptidyl-tRNA to incoming amino acid
Amphenicols	Chloramphenicol, azidamfenicol	Larger (50S) ribosomal subunit, interfere in chain elongation
Lincosamides	Clindamycin, lincomycin	Larger (50S) ribosomal subunit, interfere in chain elongation by interfering in addition of peptidyl-tRNA to incoming amino acid
Pleuromutilins	Valnemulin, azamulin	Larger (50S) ribosomal subunit, interfere in positioning of 3′-end of tRNA resulting in inhibition of peptide bond formation by peptide transferase
Others	Thiostrepton	Inhibit ribosome-dependent EF-Tu and EF-G GTPase

2.4 Metabolic Activity Inhibition

Chemicals that inhibit the essential component of the metabolism are called antimetabolites. These are used as antibiotics and inhibit the use of metabolite. These are analogues of the physiological metabolites. These analogues compete with the physiological metabolites resulting in retardation of cell growth or cell division (Brodie et al. 1958). There are three main types of antimetabolite antibiotics. The first is the antifolates which impair the function of folic acid leading to disruption in the biosynthesis of nucleotides (Kompis et al. 2005). For example, methotrexate is an analogue of folic acid, which inhibits biosynthesis of tetrahydrofolate by binding and inhibiting dihydrofolate reductase enzyme resulting in ultimate inhibition of both DNA and RNA biosynthesis (Hawser et al. 2006).

The second type of antimetabolite antibiotics consists of pyrimidine analogues which mimic the structure of metabolic pyrimidines. Three nucleobases, cytosine (C), thymine (T), and uracil (U), found in nucleic acids are pyrimidine derivatives, and the pyrimidine analogues disrupt their formation and consequently disrupt DNA and RNA synthesis (Kidwai et al. 2003).

The third type of antimetabolite antibiotics is purine analogues. They mimic the structure of metabolic purines. Two of the four bases in nucleic acids, adenine and guanine, are purines. Purine analogues disrupt nucleic acid production. For

example, azathioprine is the main immunosuppressive cytotoxic substance that is widely used in transplants to control rejection reactions by inhibiting DNA synthesis in lymphocytes (Plunkett and Saunders 1991).

There are also antimetabolites that are specific for the metabolism of certain bacteria. That makes them suitable to use as an antibiotic against that bacteria. Table 5 shows the classes of antibiotics, names, and their primary target which inhibit metabolic activity.

2.5 *Cell Membrane Alteration*

Antibiotics damage the bacterial plasma membrane resulting in leaking the cell contents and disruption of the cross-membrane potential (ionic gradients) and ultimately leads in cell death (Ernst et al. 2000). Examples of antibiotics that disrupt the cell membrane include gramicidin and polymyxin. Gramicidin is a heterogeneous mixture of six antibiotic compounds. Gramicidin stimulates the movement of monovalent cations like sodium ions through unrestricted regions since bacterial cell membrane becomes more permeable. This leads in destruction of ionic gradient across the cell membrane. Polymyxin interacts with bacterial cell wall phospholipids and damages the structure of the bacterial cell membrane (Mogi and Kita 2009). Table 6 shows the classes of antibiotics, names, and their primary target which cause cell membrane alteration.

Table 5 Metabolic activity inhibitory antibiotics

Antibiotic class	Name	Primary target
Sulfonamides and dapsone	Sulfamethazine, sulfapyridine, sulfamethoxazole, sulfadiazine, sulfamerazine, methotrexate	(1) Dihydropteroate synthase
		(2) Compete with p-amino benzoic acid (PABA) preventing synthesis of folic acid
Pyrimidine analogues	Decitabine, gemcitabine, pentostatin	DNA synthesis
Purine analogues	Azathioprine, mercaptopurine	DNA synthesis

Table 6 Cell membrane altering antibiotics

Antibiotic class	Name	Primary target
Lipopeptides	Polymyxin B	Outer membrane by binding with lipopolysaccharides
Heterogeneous peptide	Gramicidin	Ion channels in the membrane
Others	Valinomycin, nonactin, salinomycin	Membrane ionophore

3 Development of Resistance in Bacteria

Antibiotic acts as a ligand for its target which is a specific molecule of the pathogen. The binding of the antibiotic with the specific target causes killing of the pathogen. As a natural response, antibiotic resistance emerges in the pathogen population either through spontaneous changes or through acquisition of resistant genes from other microbes. Prolonged repeated use of a particular antibiotic leads to a bulk of resistant cells in the pathogen population (Heinemann 1999). The acquired resistance can be attained by any one of the following biochemical mechanisms:

3.1 Production of Drug-Inactivating Enzymes

Bacteria modify the structure of the antibiotic resulting in their protection (Alekshun and Levy 2007). They produce enzymes that destroy or inactivate the antibiotic and thus becoming resistant to that antibiotic. A bacteria becomes resistant to β-lactam ringed antibiotics by producing β-lactamase capable of breaking β-lactam ring in the antibiotic resulting in loss of antibiotic activity. For example, after breaking the β-lactam ring of penicillin, penicilloic acid produced is ineffective in binding to penicillin-binding proteins (PBPs), protecting the process of cell wall synthesis (Livermore 1995).

Some bacteria protect themselves from aminoglycoside antibiotics, viz., neomycin, netilmicin, tobramycin, gentamicin, and amikacin, by secreting a specific enzyme which transfers a specific chemical group like phosphoryl group resulting in loss of antibiotic activity (Mingeot-Leclercq et al. 1999).

3.2 Modification of an Existing Target

Antibiotics work by specifically binding on the target within the bacteria, and even slight alteration in the target may affect binding of the antibiotic on it. Bacteria develop resistance by causing alteration in the target site in the antibiotics. Some bacteria modify their target sites to avoid recognition by the antibiotic. This is the reason that sometimes even without modification in the antibiotic structure, there is no binding of it with the target site in the bacteria resulting in no inhibition (Colas et al. 2000). Change in the bacterial target site generally occurs due to mutagenic change in the gene. Lambert (2005) reported mutation of DNA unfolding enzymes and RNA synthesizing enzyme by quinolones and rifamycins, respectively.

3.3 Alternate Target Production

This mechanism of antibiotic resistance is quite specific. In this mechanism, bacteria produces a substitute target that is not attacked by an antibiotic. Meanwhile, bacteria also produces a native target that is sensitive to antibiotic. Bacteria survives as alternative target adopts the role of the native target. Growth of a specific *Staphylococcus aureus* does not get inhibited by flucloxacillin due to the presence of an additional penicillin-binding protein, PB2′, which does not bind to β-lactams (Otero et al. 2013).

3.4 Reduced Cell Permeability

Antibiotic works only when it enters the bacterial cell and reaches up to its target site where it can interfere with normal functioning of the cell. Antibiotic enters in the bacterial cell through porin channels present in its outer membrane. Therefore, some bacteria lose the porin channels which reduce the uptake of many hydrophilic drugs across the cell wall. This stops the antibiotic from entering across the bacterial cell wall. A variety of microbes which do not retain violet stain modify the cell membrane porin channel frequency, size, and selectivity that reduce the uptake of certain antibiotics, viz., aminoglycosides and β-lactam ringed. The prohibited entry prevents these antibiotics from reaching their intended targets (Nguyen and Gutmann 1994).

3.5 Drug Removal from the Cell

Antibiotics can be effective only when they are present in a certain amount at the target site. Sometimes bacteria throw out the antibiotics almost at the same rate as it can enter with the help of membrane proteins, which act as export or efflux pump. Efflux pumps can be specific to antibiotics. The continuous outward flow of antibiotic from the cell leads to the low concentration of the antibiotic which is insufficient to elicit any response. Most of the efflux pumps are multidrug transporters capable to flow outward many unrelated antibiotics. This causes multidrug resistance (Li et al. 1994; Levy 2002a).

4 Misuse of Antibiotics

Antibiotics are the important drugs. They play important role in counteracting bacterial infection(s), hinder the spread of the disease, and reduce the complication(s) if any due to that particular disease. The overuse and misuse of antibiotics are the main causes for antibiotic resistance including multidrug resistance (Patterson 2001).

Overuse of the drug is caused when an antibiotic is taken for a condition that cannot be treated like viral infection or taking wrong doses. Overuse of drug may happen because of self-prescription and selling of the drug in the open market. This is because of the lack of imposition of legislation laws that leads to the sale of the counterfeit drugs which may contain inappropriate quantities of active ingredients. Overuse may also be because of overprescribing of antibiotics by the doctor that leads to the excessive demand for antibiotics by the population which ultimately results in antibiotic-resistant microbes. It has been observed that especially in the developing countries, antibiotics are mostly prescribed empirically without confirming bacterial confirmation in the pathology/microbiology laboratory. Overuse of antibiotics affects the body's normal flora and disrupts the balance between beneficial bacteria that help digestion (Blaser 2011).

Underuse of the drug can be manifested by not finishing a course of antibiotics as prescribed (stopping the antibiotic before the infection is fully cleared from the body). In developing countries, the unavailability of the drug also leads to the truncated treatment. This leads the infection to persist and proliferate and subsequently may threaten communities with new strains of infectious bacteria. The situation becomes more difficult to cure and more expensive to treat (Gilberg et al. 2003).

Besides exploitation of antibiotics in the treatment of infection in humans, antibiotics are also commonly used in farming, animal husbandry, and aquaculture. The use of antibiotics as pesticides is also done for treating trees and other agricultural products. Besides, antibiotics are added to animal feed for mass prophylaxis against infections or for growth promotion particularly for pigs and poultry farms. The sub-therapeutic doses of antibiotics are also used in water to treat fish diseases (Smith et al. 1994). Excessive application of antibiotics in intensive agricultural and farming units particularly pig and poultry farms is found as a growing threat. This can result in resistant microorganisms, which can spread to humans. Besides, there are indications that microbial resistance may get transmitted among animals including humans through food consumption (Marshall and Levy 2011). Therefore, there is a need to cut unnecessary use of antibiotics in farming. Responsible antibiotic use in industry and good practice for patients and physicians are essential to keep resistant bacterial strains curable and antibiotic treatment affordable to patients (Phillips et al. 2004).

5 Impact of Antibiotic Resistance

It is being observed that the number of antibiotic-resistant bacteria is increasing day by day, and therefore, it has become a matter of great clinical and public health concern (Sacks and Greene 2011). Some of the impacts of the antibiotic resistance bacteria are:

5.1 Difficult to Treat Infections

Treatable diseases like pneumonia, tuberculosis, and even minor infections have become incurable because of antibiotic resistance. This leads to the economic and emotional hurdle on families and on our healthcare system. As many strains of bacteria are resistant to several commonly used antibiotics, therefore, physicians will have to think for different antibiotics on trial basis till patient gets relief (Levy 2002b; Klugman 2007).

5.2 Increased Cost and Length of Treatments

There is a correlation between spreading of antibiotic resistance, indoor stay in the nursing home/hospital, financial cost of the treatment, and diagnostics (Cosgrove 2006). As bacteria are becoming resistant to antibiotics, drugs are becoming ineffective. So the drugs are replaced with the second line of drugs that are more expensive and may have more side effects. Infection with an organism/pathogen that is resistant to multiple drugs results in expensive treatment due to the use of multiple drugs (Niederman 2001).

5.3 Increased Morbidity and Mortality

Antibiotic resistance leads to inadequate or delayed therapy for several diseases that shows adverse outcome of an infection. It also resulted in lesser probability to cure diseases in humans and other eukaryotes including plants and animals. As per Threat Report 2013 of the Center for Disease Control and Prevention, nearly 23,000 persons die annually after infections caused by drug-resistant bacteria in USA. Many more patients die of other conditions complicated by infection with resistant pathogens (Cosgrove 2006).

6 Controlling Antibiotic Resistance

Antibiotic resistance has become a worldwide worry. It is apprehended that after infection of an individual by an antibiotic-resistant microbe, there are chances of its spread in other populations also in addition to tough way of treatment. Therefore, it has become almost necessary to control the spreading of drug-resistant microbes with the judicious use of drugs for prophylaxis and treatment. Antibiotic resistance can be controlled by:

6.1 Prudent Use of Antibiotics

Uncontrolled use of antibiotics must be decreased to retain the potency of existing antibiotics. To decrease the use of these valuable drugs, physicians, pharmacists, and the public must avoid careless use. To control the spread of resistance, antibiotics must be used smartly. Physicians must prescribe antibiotics for microbial loads only and in proper dose for correct amount of time. Besides, doctors should choose narrow-spectrum drugs to avoid killing populations of beneficial bacteria along with the disease-causing bacteria. Antibiotic usage for nontherapeutic purposes in farm animals and agriculture should be discouraged (Phillips 2001; Bergeron 2014).

6.2 Infection Control

Effective infection control that impedes the growth of bacteria can be used. Measures such as cleaning of water supplies, proper sanitation, and reduced overcrowding should be taken to prevent the infection. Other personal preventative measures like frequent hand washing should be taken. It would ensure that people become lesser sick. This will lead to reduce transfer of resistant infections to others (Weinstein 2001).

6.3 Use of Vaccines

Vaccines prevent infections and reduce the need for antibiotics. The need for antibiotics can be reduced by using vaccines that may help in prevention of infections. Vaccine can be used in young children who are more vulnerable to infection. A promising solution of evolving this bacterial resistance is the development of new vaccines. Efforts must be done that vaccines be effective for a longer

period if not for lifetime. This would also be a solution to treat other infectious diseases for which there is a lack of efficacious medication (Mishra et al. 2012).

6.4 Regulations

Regulations are required for the use of antibiotics, and these may be like a doctor's prescription requirement for a patient to purchase an antibiotic. There must be mandatory requirement of the label on the antibiotic indicating that it must be taken only on the advice of a doctor and for confirmed bacterial infection only. It must not be sold without a photocopy of the prescription by a qualified doctor. Regulations must be such that punitive action must be taken against the pharmacist if found selling it without prescription (Gould 1999; Andersson and Hughes 2010).

7 Overcoming the Drug Resistance

Researchers are engaged to search alternate ways to combat antibiotic resistance which will strengthen the potency of prevailing drugs. It can be done by modifying the antibiotics in such a way that bacterial enzymes responsible to cause modify the antibiotics could not attack them. It may also be done by using additional enhancer like silver that enhances the potency of the antibiotic against gram-negative bacteria (Morones-Ramirez et al. 2013). Reactive oxygen species like superoxide can be used with drugs which can make them more effective as they affect the bacterial physiology (Kohanski et al. 2010). Physicians may be advised to prescribe "decoy" molecules along with the antibiotic. The "decoy" contains the qualities of an antibiotic but is not the actual antibiotic. The antibiotic is hidden behind the decoy molecule, and the secreted bacterial enzyme is unable to attack the antibiotic. Decoy molecules, viz., clavulanic acid, have been tried for making the secreted enzyme ineffective against the β-lactam ringed family. This is the best solution because it does not require the development of a new antibiotic. If more antibiotics are produced and new antibiotics are replacing the older ones, the bacteria will continue to grow resistance against the new antibiotic (Shamnas et al. 2013).

Another approach to solve the problem of antibiotic resistance is to interfere in the mechanism that promotes resistance instead of the attempt to kill bacteria. As an example, if a mechanism that duplicates or moves the bacteria's genetic material is interfered, then it can lead to the elimination of the transfer of resistant genes between bacteria.

8 New Antibiotic: Teixobactin

The fate of modern medicines depends on the potent antibiotics (So et al. 2010). Between 1930 and 1962, there are reports of more than 20 novel classes of antibiotics which have been discovered globally (Coates et al. 2011). These discoveries provided effective cure for many present-day known diseases. However, with increased cases of drug resistance, requirement is being felt for new compounds (Thomson et al. 2004). Almost after 30 years, in 2015 a new antibiotic called teixobactin has been found to treat many common microbial diseases, viz., tuberculosis and septicemia. Ling et al. (2015) showed its mode of action that it binds with the lipid II and lipid III which are precursors of peptidoglycan and cell wall's teichoic acid, respectively. This binding inhibits the biosynthesis of bacterial cell wall.

Teixobactin has been found in soil bacteria and using a high-throughput screening device called the iChip. The iChip has many plates with a large number of wells covered by twofold of semipermeable membranes. It is used for concurrent isolation and growth of uncultured microbes. Teixobactin is produced from the bacteria named *Eleftheria terrae*. Teixobactin has been found effective on mice infected with specific *S. aureus*, antibiotics tolerant strains of *Mycobacterium tuberculosis* and *Streptococcus pneumonia*. The properties of this compound may be exploited in developing new antibiotics likely to avoid development of resistance.

9 Databases and Tools

9.1 CARD

It is a database available at http://arpcard.mcmaster.ca. This database includes a variety of data that describe the resistance genes and associated proteins, antibiotics and their target, and literature concerning antibiotic resistance. CARD is updated continuously and curated using concurrently published data and continuous increasingly Antibiotic Resistance Ontology (ARO). At present, CARD is having a sequence of over 1600 antibiotic-resistant genes. It is integrated with other resources like NCBI and PDB. This may be used for searching all publications related to gene annotations, ontology, and connections with other online databases (McArthur et al. 2013).

9.2 ARDB

Antibiotic Resistance Genes Database (ARDB) contains data about tolerance and nucleic acid sequences annotated with much information regarding linkages to

other nucleic acid and protein sequence databases, CDD annotations, COG, ontology, tolerance profile, mode of action, etc. It can be accessed from http://ardb.cbcb.umd.edu/. Till last update, this database has details for 23,137 tolerant genes, 632 genomes, 267 genera, 1737 species, and 2881 vectors and plasmids. Users can access the ARDB either by keyword search and browsing or by BLAST. Any user can identify and annotate new antibiotic-tolerant genes by blasting ARDB sequences. For that, one may use regular BLAST and/or RPS-BLAST tools available within the ARDB database (Liu and Pop 2009).

9.3 ARGO

ARGO stands for Antibiotic Resistance Genes Online that is featured to collect and archive antibiotic-resistance genes in bacteria. The current version of ARGO includes genes that are responsible for resistance to tetracycline, β-lactams, and vancomycin. It is available at http://www.argodb.org/. The ARGO can be searched either by sequence, gene finder, or classification of antibiotic. It is having links of APUA, ROAR, CDC, NRSA, EARSS, and VRSA databases and many more (Scaria et al. 2005).

9.4 MvirDB

It can be accessed at http://mvirdb.llnl.gov/. This contains detailed information regarding microbial virulence factors, antibiotic-tolerant genes, and proteinaceous toxins. The MvirDB collects data from various other online sources like SCORPION, Tox-Prot, the PRINTS virulence factors, VFDB, TVFac, ARGO, Islander, and subset of VIDA. MvirDB provides BLAST tool that can be used to align sequences of proteins and nucleic acids within it. To access the useful information, user can use browser tool. This database has automated system that updates the database weekly. It is having fast annotation system that automatically annotates protein entries (Zhou et al. 2007).

9.5 ARG-ANNOT

This is a tool which identifies the prevailing and suspected new antibiotic-tolerant genes in microbial genomes. It uses local blast program in Bio-Edit software to analyze sequences without user interface. Information required regarding antibiotic-tolerant genetic determinants to run the tool is taken from the literature and databases. To test the software, a database has been built that included 1689 antibiotic-resistant genes. Web interface for ARG-ANNOT is available on http://en.

mediterranee-infection.com/article.php?laref=283%26titre=arg-annot-. This link provides access to Bio-Edit and other tools for BLAST and post-BLAST analyses and tutorials to create a local database (Gupta et al. 2014).

9.6 ResFinder

ResFinder identifies acquired antimicrobial-resistant genes in total or partial sequenced isolates of bacteria. It is publically accessible at https://cge.cbs.dtu.dk/services/ResFinder/. ResFinder is updated continuously for newly identified antibiotic-tolerant genes. The tolerant genes can be identified for one or more antimicrobial classes at a same time using BLAST. ResFinder was created using 1862 sequences having 1411 antibiotic-tolerant genes and 23 de novo-sequenced isolates from which it identifies the acquired resistant genes. ResFinder is a web server that easily identifies the acquired antibacterial-tolerant genes in sequenced isolates (Zankari et al. 2012).

10 Conclusion

Development of antibiotic resistance has limited our repertoire of effective drugs, which creates a problematic situation to treat the bacterial infections. This threatens the effective prevention and treatment of resistant microbes.

Hence, there is a requirement of action in society and all government sectors. Although antibiotic resistance is a natural phenomenon, it is rapidly spreading due to human activities. Activities like misuse of antimicrobial drug in animal husbandry and farming support the disclosure and assemblage of antibiotic-tolerant strains. In addition, low-quality preventive measures and ways to curb menaces also aid in development of antibacterial tolerance. As antimicrobial resistance is rapidly growing, it will cause difficulty in treating bacterial infection, and there will be increased cost and length of treatments and more side effects because of the use of multiple and more powerful medications. Resistance can be overcome by strengthening the existing antibiotics either by using an additional molecule or to interfere with the mechanisms that promote resistance. Research is needed to find the best strategies for the optimal use of antibiotics and to find the novel class of antibiotics. To enhance research about antibiotics, various databases and tools are available containing data from bacterial population, genomics, drugs, mechanism of action, ontology, COG, CDD annotations, and many more. Now it is being realized that antibiotics must be taken as special category medicines, and efforts must be done to protect them as these are the wealth for humanity.

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