



Recent Approaches and New Challenges of Antibiotics

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ABSTRACT

Antibiotics are the chemical agents that will prevent bacterial growth by stopping the bacterial cell from killing (bactericidal) or by dividing them (bacteriostatics). So, antibiotics are the essential part of medicines used for both animals and human health. In 1990s the antibiotics were first discovered to fight against microorganism. Based on their chemical structures the antibiotics are grouped into several classes. For several decades, antibiotics have been critical in fight against infectious diseases caused by bacteria and other microbes. Wound infections, tuberculosis, pneumoniae, gonorrhoea, viral infections such as common cold, flu, cough are just a few of the diseases that are treated with antibiotics. The antibiotics therapy for emerging hard to treat multidrug-resistant bacterial infections is limited, resulting in high morbidity and mortality worldwide. Apparently most pathogenic microorganisms have the capability of developing resistance to atleast some antimicrobial agents. The main mechanisms of resistance are: limiting uptake of drug, modification of a drug target, inactivation of a drug and active efflux of a drug. Drug resistant infections are on the rise everywhere, and threatening public health on a major portion, the discovery of novel antibiotics capable of countering the counter-attack by these organisms has become an emergency. Urinary tract infections, newborn infections and chemotherapy, to take just a few instances, are becoming rapidly unsafe because of the lack of working antibiotics to counter just five bacteria, including *Escherichia coli* (E. coli), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Klebsiella pneumoniae*. Drug resistant tuberculosis is another big challenge, with over half a million cases at present, posing a high risk of infections to children. Even when novel antibiotics are developed, eventually resistance should crop up to them as well, making it significant to constantly come up with new preventive and diagnostic methods, as well as control and surveillance of contagious infections.

Keywords: Antibiotics, Antimicrobial resistance, Infections, Mechanism of action, Resistant.

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2. Bactericidal (e.g. aminoglycosides, beta-lactams, vancomycin, quinolones, rifampin, metronidazole)

Action on Bacteria

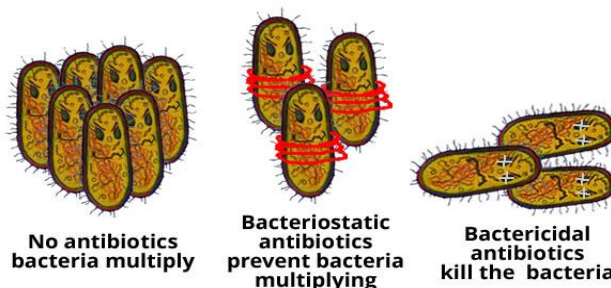


Figure 1: Action on bacteria

INTRODUCTION

Antibiotics are the chemical agents that will prevent bacterial growth by stopping the bacterial cell from killing (bactericidal) or by dividing them (bacteriostatics). So antibiotics are the essential part of medicines used for both animals and human health.¹ In 1990s the antibiotics were first discovered to fight against microorganism. Based on their chemical structures the antibiotics are grouped into several classes. For several decades, antibiotics have been critical in fight against infectious diseases caused by bacteria and other microbes. The actions on bacteria are of two types shown in **figure 1**.

1. Bacteriostatic (e.g. chloramphenicol, erythromycin, clindamycin, sulfonamides, trimethoprim)

The term antibiotic literally 'opposing life,' is derived from Greek roots anti means "against" and bio means "life"-is broadly used to refer to any substances which is used against microbes, in general medical usage, antibiotics such as penicillin which are produced naturally by one microorganism fighting with another, whereas non antibacterial such as sulfonamides and antiseptics are fully synthetic. Antibiotics are given to human beings for treatment and Prophylaxis of infectious diseases, about



80% to 90% of antibiotics which are used in outpatients and remaining used in hospitals purpose.^{2,3} Antibiotics are generally appear to be used not only excess but also inappropriately. There are four main types of resistance to antibiotics develops;

1. Natural (Intrinsic) resistance.
2. Acquired resistance.
3. Cross-resistance.
4. Multi-drug resistance and pan-resistance.

History

Penicillin is the first antibiotics was discovered in 1929 by Sir Alexander Fleming, it is used to treat the bacterial infections especially those caused by Staphylococcus and Streptococci without harming the host⁴. A messy man Alexander Fleming who discovered accidentally penicillin by nature. In 1928, upon returning from holiday in Suffolk he noticed that a fungus, *Penicillium notatum*, had contaminated a culture plate of staphylococcus bacteria he had accidentally left uncovered. Alexander Fleming found that *P. notatum* proved that even at very low concentrations, shows the extremely effectiveness by preventing staphylococcus growth even when diluted 800time, and was less toxic than the disinfectants used at the time. Fungus will create the bacteria-free zones wherever it grew on the plate Flemingated and grew the moulding pure culture. After penicillin gained extensive use in the 1940s antibiotic resistance first became most challenging⁵. Even after early trails in treating human wounds British pharmaceuticals companies by collaborating ensures that the mass production of penicillin (the antibiotic chemical produced by *P. notatum*) was possible. A fire accident Boston MA, USA, in which nearly 500 people died, many of the people received skin grafts which are liable to infection by staphylococcus.⁶ By treating with penicillin was hugely successful, and by seeing this an US government began supporting the mass production of the drug. In 1994 penicillin was being widely used treat the infections both in the fields and hospitals throughout Europe. The nickname of penicillin is 'the wonder drug' was given by the end of World War II, had saved many lives. For, millennia to treat infections antibiotics are widely used although they did not know the infections were caused by bacteria for so people until the last century. The early 1950s and last 1940s they saw the discovery antibiotics such as Streptomycin, chloramphenicol, tetracycline and antibiotic chemotherapy age came into full being. A German physician, who was called as Paul Ehrlich noted that certain chemical dyes colored by some bacterial cells but not others.⁷ Paul Ehrlich discovered that a chemical called arsphenamine in 1909 which shows effective treatment for syphilis. That although became the first modern antibiotic, although Ehrlich himself referred to his discovery as 'chemotherapy' - the use of a chemical to treat a disease.⁸ The people doesn't know that the infections is caused by certain bacteria until the 20th century, infections that we

now consider directly to treat such as pneumonia and diarrhea which is caused by bacteria, were the number one cause of human death in the developed world. 'Antibiotic' is the word was first used over 30 years later by the Ukrainian- American inventor and microbiologist over 20 antibiotics in his lifeline.

Mechanism of action of antibiotics

The most common mechanisms of action is targeting the cell wall, which are present in prokaryotic cells such as bacteria and absent in eukaryotic cells such as human. Thus, antimicrobial agents act choosily on vital microbial functions with minimal effects or without affecting host functions. There are different classes of antibiotics possess specific modes of action by which they inhibit the growth or kill bacteria.⁹ shown in **Figure-2**.

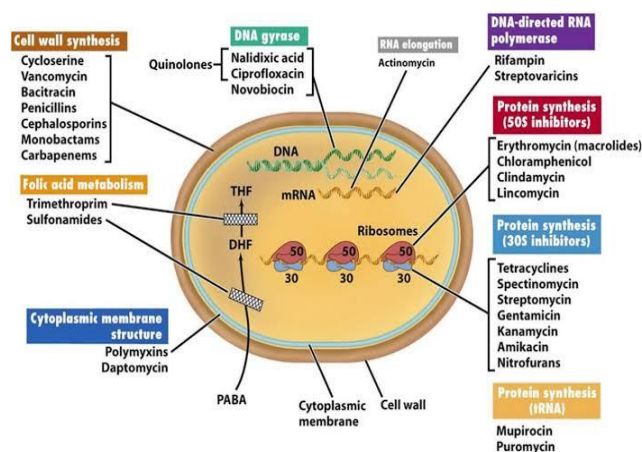


Figure 2: Mechanism of action of antibiotics

Mode of action of antibiotics

Mode of action of action of antibiotics can be distinguished on the basis of their ability to interfere with their metabolic machinery of microbes. These microbes need this machinery to thrive, and to hold itself together, or make duplicate versions of microbes. Antibiotics are supposed to thwart bacterial –not human –cells through one or more of the following mode of action;

Mode # 1- interference with microbial activity to make cell walls.

The mode of action is a common requirement for these organisms to cause infections for without any rigid support of the cell wall, almost all the bacteria simply break open and die or collapse into it, an effective heap. However, a few varieties of bacteria can actually thrive by the constructing outer membranes instead of cell walls, but they are rarely can reproduce to create further harm. The antibiotics of key molecular target are a substance called mucopeptide which coats the bacterial membrane and gives it its rigidity.

Examples include such narrow – spectrum antibiotics as:

- Penicillin and its derivatives;
- Cephalosporins.

Penicillins and Cephalosporins can activate peptidases with a key bacterial enzyme that are synthesize the rigid cellular walls, and these are all the more effective the thickening the walls. They are remarkably non-toxic at normally and are used therapeutic dosages because they are made from different materials than bacteria.

Mode # 2- inhibition of protein synthesis.

These are generally more toxic to the human body, than the orders and include the broader-spectrum antibiotics such as:

- Chloramphenicol, is the most potent extraordinary antibiotic but also an extremely toxic one is used for cells of the bone marrow and also causing blood disorders as granulocytosis, pancytopenia. And that so-called "grey syndrome" (weakness, listlessness, gray pallor, hypotension in treated newborn, especially premature Infants). Because of this toxicity, chloramphenicol is kept especially for a particular person. For serious diseases (typhoid fever, bacterial meningitis).
- Tetracycline which are derived from the broadest spectrum in this category. Tetracycline is less toxic than chloramphenicol, tetracycline as enthusiasm

binds to calcium, magnesium and other essential minerals in meningitis.

- Polymirin (B and E forms): Relatively non-toxic, and available as a topical non-prescription-drug.
- Erythromycin.

Mode # 3- interference with protein or membrane synthesis.

In this mode it may involve both aerobic and anaerobic bacteria. And these antibiotics may include the cephalosporins.

Mode # 4- interference with genetic synthesis or operation (DNA or RNA).

These include: Aminoglycosides.

Mode # 5-interference with the metabolic reactions.

These include: Trimethoprim, Sulfonamides.

Mode # 6-combination modes.

At the different places two or more chemicals interfere with the same reaction. Examples include: Trimethoprim, Sulfamethoxazole.

Table 1: A list of antimicrobial agents and their modes of action

Antimicrobial agents	Group	Mode of action
Ampicillin, Augmentin, Amoxicillin	Penicillin	Inhibitor of cell wall synthesis
Ceftriaxone	Cephalosporins	Inhibitor of cell wall synthesis
Chloramphenicol	Chloramphenicol	Inhibitor of protein synthesis
Erythromycin, Azithromycin	Macrolides	Inhibitor of protein synthesis
Gentamycin, Streptomycin	Aminoglycosides	Inhibitor of protein synthesis
Oxytetracycline	Tetracycline	Inhibitor of protein synthesis
Nalidixic acid, Ciprofloxacin	Quinolones	Inhibitors of DNA synthesis
Sulfamethazine, Trimethoprim	Sulfonamides	Competitive inhibitors of folic acid synthesis

Antibiotic resistance

Antibiotics resistance is the ability of microorganism or bacterium to reproduce and survive in the presence of antibiotic doses that were previously thought effective against them.¹⁰ Antibiotic resistance genes of origin are unclear; however, studies using clinical isolates collected before the introduction of antibiotics demonstrated susceptibility, although, conjugative plasmids were present.¹¹ Antimicrobial resistance bacterial pathogens is a worldwide challenge related with high morbidity and mortality. In Gram-positive and Gram-negative bacteria of multidrug resistant pattern have resulted in difficult-to-treat or even untreated infections with conventional antimicrobials. Because these early identification of original microorganisms and their antimicrobial susceptibility patterns in patients with bacteremia and other serious infections is insufficiency in many healthcare settings,

broad spectrum antibiotics are liberally and mostly unnecessarily used. Sensational increases in emerging resistance occurs and, when coupled with poor infection by the control practices, resistant bacteria can easily be disseminated to the other patients and the environment.¹² Resistance is defined as bacteria that are not inhibited by usually achievable systemic concentration of an agent with normal dosage schedule and / or fall in the minimum inhibitory concentration ranges. Likewise the multiple drug resistance is defined as when resistance of two or more drugs or drug classes.¹³ Cross resistance is defined as acquisition of resistance to one antibiotic conferring resistance to another antibiotic, to which the organism has not been exposed. 'antimicrobial-resistant' or 'drug-resistant' are terms of microorganisms when they are no longer inhibited by an antimicrobial to which they were earlier sensitive such resistance are called 'acquired



resistance' and is encoded by resistance genes in the DNA of the microbe. These genes can antimicrobial resistance also transfer from drug-resistant microbes to drug sensitive ones. By the today, on the one hand trying to develop new drugs, on the other hand, there are many difficulties in treatment as a result of development of resistance to these drugs rapidly. The major public health problem in all over world is to develop the resistance to antibiotics.

Types of Antibiotics - Resistant Infections

a. methicillin-resistant staphylococcus aureus

The most common pathogen found on the skin or in the nose of healthy people is staphylococcus. In the most of the time, these bacteria are harmless, but when they enter a wound they can cause an infection. This type of bacteria can resistant to many antibiotics, including methicillin.

b. streptococcus pneumoniae

Streptococcus Pneumoniae bacteria cause many types of illness, including pneumonia, a lung infection. These bacteria can also lead to ear and sinus infections, as well as meningitis, an infection of the membranes around the brain and spinal cord. Bacteremia, a blood stream infection, can also be caused by streptococcus pneumoniae

c. carbapenem-resistant enterobacteriaceae

Family of bacteria is enterobacteriaceae which include pathogens found in the digestive tract as well as the environment, including Escherichia coli (E.coli), salmonella, and shigella among others.

Mechanism of Antibiotic Resistance

Mechanism of antimicrobial resistance can be divided into four main categories:(1)limiting uptake of a drug (2) medication of a drug target (3) inactivating a drug (4) active drug efflux. Intrinsic resistance which can may make use of limiting uptake, drug inactivation and drug efflux; whereas in the acquired resistance mechanisms used may be drug target modification, drug inactivation, drug efflux. Because of differences in structure, etc., there is variation in the types of mechanisms used by gram negative bacteria versus gram positive bacteria shown in **figure 3**.

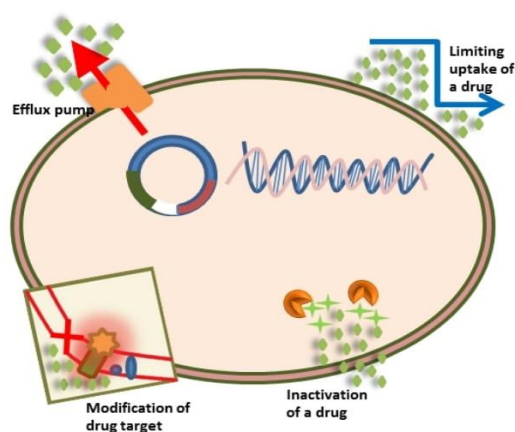


Figure 3: General antimicrobial resistance mechanisms.

(1) Limiting uptake of a drug: There is a natural difference in the ability of bacteria to limit the uptake of antimicrobial agents. The structure and functions of the LPS layer in gram negative bacteria provides a barrier to certain types of molecules.¹⁴ Certain bacteria modify their cell membrane porin channels; there by preventing the antimicrobials from entering in to the cell. There are two main ways in which porin changes can limit drug uptake: a decrease in the number of porins present, and mutations that change the selectivity of the porin channel.¹⁵ This strategy had been observed in many gram positive bacteria such as Pseudomonas, Enterobacter and Klebsiella species against drugs such as imipenem, aminoglycosides and quinolones. Gram positive bacteria, staphylococcus aureus, recently had developed resistance to vancomycin. Of the two mechanisms that S.aureus uses against vancomycin. S.aureus produce a thickened cell wall which makes it difficult for the drug to enter the cell and provides an intermediate resistance to vancomycin. These strains are designated as VISA strains.^{16,17}

(2) Modifying of a drug target: Modification of the antibiotic target site makes the antibiotic unable to bind properly. Microorganisms cannot evade antimicrobial action by dispensing with them entirely because of the vital cellular functions of the target sites. In this mechanism, bacteria found ways to alter of antimicrobial agents. The classical example of drug target modification is the staphylococcal mechanism of variously altering the penicillin Binding protein (PBP) which is the target of Beta-lactam antibiotics.¹⁸

(3) Inactivating a drug: On some occasions cell may gain resistance to antibiotics is by making an enzyme that renders the drug inactive, or that decreases the functionality of the antibiotics. The best example is beta lactamase which has capable of breaking the beta-lactam rings of beta lactam antibiotics such as penicillin. In such manner, the breakage of the beta-lactam ring stops the antibiotic from being able to attach to the peptidoglycan precursors. But it will be less likely that penicillin or other similar drugs will be able to disrupt the integrity of the cell wall, as long as the organism produce beta lactamase.¹⁹ This method of resistance can be transferred from one bacterium to another through the production of the R-plasmids, and is common in strains of methicillin resistant Staphylococcus aureus (MRSA).²⁰

(4) Active drug efflux: Bacteria possess chromosomally encoded genes for efflux pumps. Some are expressed constitutively, and others are induced or overexpressed (high-level resistance is usually via a mutation that modifies the transport channel) under certain environmental stimuli or when a suitable substrate is present. The efflux pumps function primarily to rid the bacterial cell of toxic substances, and many of these pumps will transport a large variety of compounds (multi-drug [MDR] efflux pumps). Most of the bacteria possess many different types of efflux pumps in bacteria classified based on structure and energy source:

1. The ATP-binding cassette (ABC) family,
2. The multidrug and toxic compound extrusion (MATE) family,
3. The small multidrug resistance (SMR) family,
4. The major facilitator superfamily (MFS), and
5. The resistance-nodulation-cell division (RND) family.

Efflux pumps found in gram positive bacteria may confer intrinsic resistance because of the chromosome (natural). There are also gram positive efflux pumps known to be carried on plasmids (aquarid). These pumps include members of the MATE and MFS families. Efflux pumps found in gram negative bacteria are widely distributed and may come from all five of the families, with the most clinically significant pumps belonging to the RND family.^{14,21} shown in **Figure 4**.

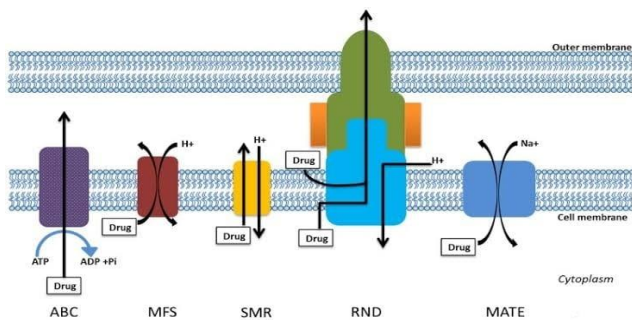


Figure 4: General structure of main efflux pump families.

Table 2: Examples of antibiotics.

Year	Antibiotic	Year	Antibiotic
1911	Arsphenamine	1987	Ciprofloxacin
1935	Prontosil	1988	Azithromycin
1936	Sulfanilamide	1988	Rifapentine
1940	Sulfamethazine	1989	Moxifloxacin
1942	Benzyl penicillin	1990	Clarithromycin
1944	Streptomycin	1992	Fleroxacin
1948	Chlortetracycline	1992	Rufloxacin
1949	Chloramphenicol	1993	Levofloxacin
1950	Penicillin G procaine	1993	Nadifloxacin
1952	Erythromycin	1994	Cefepime
1955	Tetracycline	1996	Meropenem
1955	Vancomycin	1999	Quinupristin
1958	Colistin	2000	Linezolid
1960	Metronidazole	2001	Telithromycin
1961	Ampicillin	2003	Doripenem
1961	Trimethoprim	2005	Tigecycline
1964	Gentamycin	2005	Doripenem
1964	Cefalotin	2009	Telavancin
1967	Nalidixic Acid	2010	Ceftaroline
1968	Clindamycin	2011	Fidaxomicin
1972	Minocycline	2013	Telavancin
1977	Cefadroxil	2014	Tedizolid
1980	Piperacillin	2014	Dalbavancin

1981	Co-amoxiclav	2014	Ceftolozane/Tazobactam
1982	Ceftriaxone	2015	Ceftazidime/avibactam
1985	Cilastatin	2017	Meropenem/vaborbactam
1985	Ofloxacin	2019	Imipenem/cilastatin/relebactam
1986	Mupirocin	2019	Cefiderocol

Course of time of antibiotics

Antibiotics are recommended for adults is 5 to 7 days. This is supported by a systemic review showing no significant difference in outcomes between 3-7days of antibiotics compared to 7 days or longer.²² For children with non-severe pneumonia there is no difference between 3 versus 5days of antibiotics.

Amoxicillin course of time: Amoxicillin which may come as a capsule, a tablet, a chewable tablet, and as suspension which is taken by mouth. It is usually taken every 12hours that means twice a day or every 8 hours i.e. three times a day with or without food. Treatment time length depends on type of the infection.

How long should you take a course of antibiotics?

Almost antibiotics should be taken for 7 to 14 days. In some of the cases, shorter treatments work just as well. Best length of treatments will be decided by Physician/doctor based on the infections and which is the correct antibiotic type.

Can we take two antibiotics together at the same time?

Yes, we can take two antibiotics together. In some of the infections combination of antibiotics can be taken to deal with difficult infections, but your case is rather different as you have two separate infections.

Example: Flucloxacillin for a wound infection together and Cephalexin for cystitis

Staphylococcus is a genus of gram positive bacteria, the wound infection is caused by staphylococcus. Sometimes a bacteria is resistant to simple Penicillins, and in some of the more powerful flucloxacillin is chosen. But bladder infection is caused by the different bacteria which may not respond to the penicillin, and in such a case a cephalosporin such as cephalexin the main risk is that you might get a problem with your bowel. The broad-spectrum effect of these antibiotics kill off all the 'good' bacteria. Pseudomembranous colitis is a condition in which can be quite severe and can be brought a wide range of broad spectrum antibiotics. This is a rare problem, so don't be alarmed. But if you get really bad diarrhea.

What happens if you take two antibiotics at the same time?

There is an increased risk of side effects of when we take 2 doses nearly together than recommended. When we are accidentally taking 1 extra dose of your antibiotic which is unlikely it will cause you any serious harm. But it increases they might have a chance of getting side effects, such as pain in your stomach, diarrhea, and feeling or being sick.²³



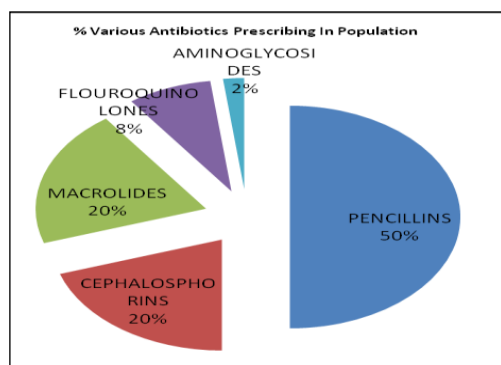
How antibiotics work on recent diseases

1. Chloroquine and hydroxychloroquine (Ex: HCQS 400 mg) are closely related antibiotics used to treat malaria and rheumatology conditions. China and France, some of the studies provided possible benefits against pneumonia caused by COVID-19 but need confirmation through randomized trails. There are many of the trails going on now to test the efficacy of these drug.

2. Chloramphenicol is an antibiotic. It is used to treat eye infections and also ear infections. But in most of the countries have banned the chloramphenicol for used in food animal production, FAO (food and agriculture organization) said. Chloramphenicol cause a serious diseases in people called “aplastic anemia”.

3. Macrolides is an antibiotic which provide the best coverages for the most likely organisms in community-acquired bacterial pneumonia (CAP). Macrolides have effective coverage for gram-positive, legionella, and mycoplasma organisms.

4. Azithromycin is an antibiotic. It's generally used to treat chest infections such as pneumonia, infections of the nose, skin infections, and some sexually transmitted infections. Azithromycin is readily taken up into atherosclerotic plaque we and others have found it to be effective in animal models.



Graph 1: Pie diagram showing the percentage of various antibiotics prescribing in study population.

Administration of Antibiotics

There are many different routes of administration for treatment of antibiotics. Antibiotics are usually taken by mouth (cefixime 200 mg). But in some severe cases, particularly deep-seated systemic infections (Pencillins), antibiotics can be given intravenously or by injection.

CONCLUSION

The truth is that bacterial are very versatile and adaptive. Antibiotics are extensively used for the both animals and human health practice in developing and developed countries of the world mainly for control and treatment of various diseases. On our own skin surface and lining our alimentary tract, we are populated by trillions of the microorganisms some of which are protective and beneficial. Their survival can be arrested to their growth inhibited with antibiotics (natural or synthetic). Antibiotic

resistance is rising to dangerously high levels in all the parts of the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases. Infections caused by antibiotic-resistant germs are difficult, and sometimes impossible to treat. These all are coupled with rapid spread of resistant bacteria. Consequently, morbidity, mortality, costs of treatment, loss of production in animals. The mechanisms described here are as varied as the bacteria themselves.

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