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ANTIBIOTICS: HISTORY AND CHALLENGES

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ABSTRACT

This article provides a brief history of antibiotics from discovery to the emergence of antibiotic-resistant infections. Antimicrobial drugs selectively kill invading microorganisms without harming host cells. Resistance to antibiotics has emerged in all known classes of natural and synthetic compounds. The review explores the origin, development, and current state of antibiotic resistance, regulation, and challenges. Understanding the mechanisms of resistance and the chemical nature of antimicrobial agents is crucial in enhancing the efficiency and lifespan of antibiotics.

KEYWORDS: Antibiotic, History, Classification, Mechanism of Action, Resistance, etc.

INTRODUCTION

In 1889, Paul Vuillemin created the term "antibiotic" by combining "anti" meaning against and "bios" meaning life, to refer to the phenomenon of one organism destroying another to protect itself. In 1942, Waksman expanded the definition of antibiotics to include chemical compounds that are derived from or produced by microorganisms and selectively suppress the growth or kill one or more species of microorganisms at very low concentrations.[1] Antibiotics have been used for growth promotion in agricultural animals in the US and other countries for 50 years.[2]

Antibiotics are a wide range of medicines that help combat bacterial infections in living systems. Initially known as "classical antibiotics," their effectiveness has decreased over time due to prolonged bacterial resistance. Consequently, new and advanced forms of antibiotics

have been discovered.[3] Peptide antibiotics have been in use for the last 30 years due to their rapid mechanism of action and low chance of resistance.[4] These antibiotics have a direct impact on the cell membrane, making them highly effective against pathogens, particularly bacteria. However, the excessive use of antibiotics in adults has led to pathogens developing resistance, which is a concerning situation that can weaken an individual's immune system.[5]

Antibiotics can either kill or halt the growth of microorganisms, allowing the body's natural defenses, like the immune system, to eliminate them. They work by stopping the synthesis of bacterial cell components, such as proteins, DNA, RNA, or by disrupting the cell membrane or other specific actions.[6] Antibiotics can also enter bacterial cell walls by binding to them and using the energy-dependent transport mechanisms in ribosomal sites, which ultimately results in the inhibition of protein synthesis.[7]

In recent decades, antibiotics have been widely used not only for human therapies, like treating infectious diseases such as COVID-19, transplants, chemotherapy, and surgeries, but also in aquaculture, animal husbandry, and agriculture to enhance crop production.[8,9] However, the overuse and delayed metabolism of antibiotics have resulted in the release of their residues into aquatic environments, causing persistent pollution.[10]

HISTORY

Penicillin, which is the first antibiotic, was discovered by Sir Alexander Fleming in 1928. However, it was introduced as a treatment for bacterial infections only in 1942. In the 1930s, Prontosil, a sulfonamide developed by the German biochemist Gerhard Domagk, was the first commercially available antibacterial. Thanks to the efficient purification and scaled-up production of penicillin by Florey and Chain, it was introduced on a large scale in 1945 as a treatment for bacterial infections. This marked the beginning of the "Golden-era" of antibiotics from 1940-1962. Scientists in Oxford played a crucial role in developing the mass production process, and Howard Florey and Ernst Chain shared the 1945 Nobel Prize in Medicine with Alexander Fleming for their contribution to creating the first mass-produced antibiotic. Most of the antibiotic classes used as medicines today were discovered and introduced to the market during this era. Each class usually contains several antibiotics that have been discovered over time or are modified versions of previous types. For instance, there are numerous examples of B-lactams (pronounced ß-lactams) such as different penicillins and cephalosporins.

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Classification of Antibiotics

Classification of antibiotic based on the mechanism of action and chemical structure/nature of compound are following.

❖ **Classification according to their Chemical Structure.**

A. Beta- lactam antibiotics.

1. **Penicillins:** e.g. Ampicillin, Amoxocillin, Carbenicillin, Cloxacilin
2. **Cephalosporins:** e.g. Cephalexin, Cefixime, Cefazolin, Cefoxitin, Cefepime
3. **Carbapenams:** e.g. Imipenam, Meropenam, Ertapenam
4. **Monobactams:** e.g. Azetreonam

B. Aminoglycoside Antibiotics: - e.g. Streptomycin, Gentamycin, Neomycin

C. Tetracycline Antibiotic

1. **Short acting:** e.g. Oxytetracyclin, Chlortetracycline
2. **Intermediate acting:** e.g. Lymecycline, Methacyclin
3. **Long acting:** e.g. Doxycycline, Minocycline

D. Peptide Antibiotics: e.g. Vancomycin, Teicoplanin

E. Macrolide Antibiotics: e.g. Erytghromycin, Azithromycin, Clarithromycin

F. Lincosamide Antibiotics: e.g. Clindamycin, Lincomycin

G. Unclassified Antibiotics: e.g. Chloramphenicol, Rifampin, Mupirocin

❖ **Classification according to their mechanism of action**

A. Drugs that Inhibit Cell Wall Synthesis: e.g. Beta- lactam antibiotics (Penicillin, Cephalosporins, Monobactam, Carbaphenam), Cycloserine, Vancomycin, Bacitrin, etc.

B. Drugs affect Cell Membrane: e.g.

1. **Polypeptides** (Polymyxins, Colostin, Tyrothricin)
2. **Polyene** (Amphotericin B, Nystatin)
3. **Azoles** (Ketaconazole, Fluconazole)

C. Drugs that Inhibit Protein Synthesis: e.g. Tetracycline, Chloromphenicol, Erythromycin, Clindamycin, Linezolid, etc.

D. **Drugs that alter Protein Synthesis by Misreading of mRNA code**: e.g. Aminoglycosides, etc.
E. **Drugs that Inhibit DNA Synthesis:** e.g. Acylovir, Zidovudine, etc.
F. **Drugs that Affect DNA Function:** e.g. Rifampin, Metrinodazole, etc.
G. **Drugs that Inhibit DNA Gyrase:** e.g. Nalidoxic acid, Fluoroquinolones, etc.
H. **Antimetabolites:** e.g. Sulphonamides, Sulfones, Dapsone, Trimethoprim, Pyrimethamine, Ethambutol, etc.

Mechanism of Action of different Antibiotics

The mechanism of action of antimicrobial agents can be categorised based on the function that is affected by the agents, these generally included the following: inhibition of the cell wall synthesis, or nucleic acid synthesis, inhibition of ribosome function, or cell membrane function and inhibition of folate metabolism.

1.β-lactam antibiotics

β-lactam antibiotics are one of the earliest forms of antibacterial agents. They are a broad class of antibiotics that contain a β-lactam ring in their molecular structure, which includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems. These antibiotics work by irreversibly inhibiting the enzyme transpeptidase, which bacteria use to build their cell walls. Penicillin binding proteins (PBPs), which are a type of transpeptidase, bind to the end of muropeptides known as D-Ala-D-Ala to crosslink the peptidoglycan. β-lactam antibiotics mimic this site and competitively inhibit PBP crosslinking of peptidoglycan.[11] (As shown in figure no.1).

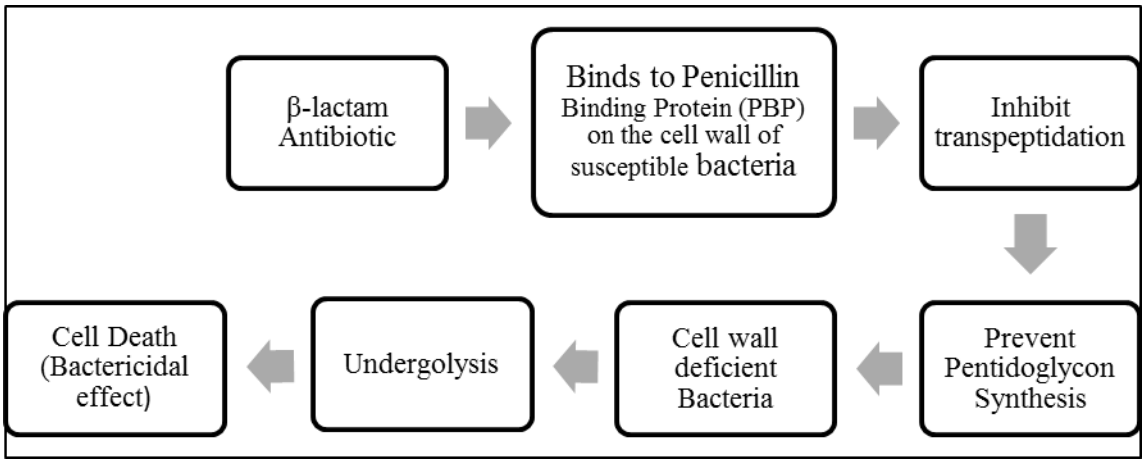

Figure No. 1: Mechanism of action of beta – lactam antibiotic.

2. Aminopenicillin

Aminopenicillins are antibiotics in the penicillin family with a β-lactam ring, which is important for their function. Amoxicillin is often combined with clavulanic acid to broaden its spectrum of action against microorganisms and overcome bacterial resistance. Clavulanic acid inhibits bacterial β-lactamase enzyme and restores the antimicrobial activity of β-lactam antibiotics.[12] (As shown in figure no.1)

3. Cephalosporins

Cephalosporins are a type of broad-spectrum antibiotic that belong to the second major group of β-lactams. They were discovered by Brotzu in 1948, who isolated them from a strain of Acremonium chrysogenum.[13] Like aminopenicillins, cephalosporins are β-lactam antibiotics and have similar mechanisms of action and resistance. However, the cephalosporin nucleus can be modified to create different antimicrobial properties. Semi-synthetic cephalosporins are categorized into four generations based on their antimicrobial activity.[14] Each newer generation has stronger Gram-negative antimicrobial properties than the previous one, but often has decreased activity against Gram-positive organisms. The fourth-generation of cephalosporins, however, has true broad-spectrum activity. (As shown in figure no.2)

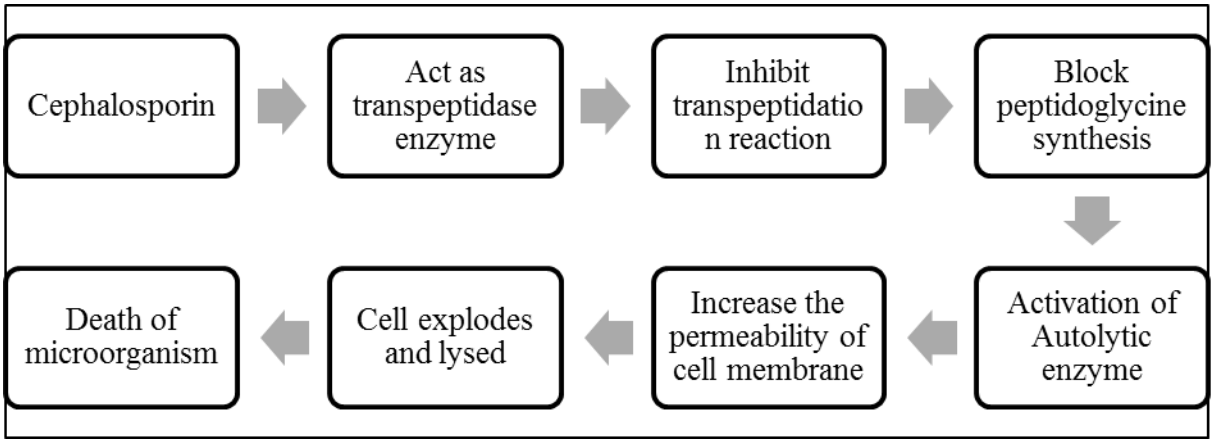

Figure No. 2. : Mechanism of action of Cephalosporins.

4. Aminoglycosides

Aminoglycosides are an important type of antibiotics used to treat Gram-negative infections, especially those caused by aerobic bacteria. They can also work together with other antibiotics to fight certain Gram-positive organisms.[15] However, their usefulness is limited by their potential toxicity and the presence of residues in food animals.

These antimicrobial compounds are produced by certain strains of Streptomyces spp., Micromonospora spp., and Bacillus spp. Examples of aminoglycosides include neomycin, streptomycin, and kanamycin. Neomycin is made up of a mix of neomycin A and B, while other members of this group are paromomycin and framycetin.

Aminoglycosides are aminocyclitols that kill bacteria by binding to the 16S rRNA and inhibiting protein synthesis. They also disrupt the integrity of bacterial cell membranes.[16] (As shown in figure no.3).

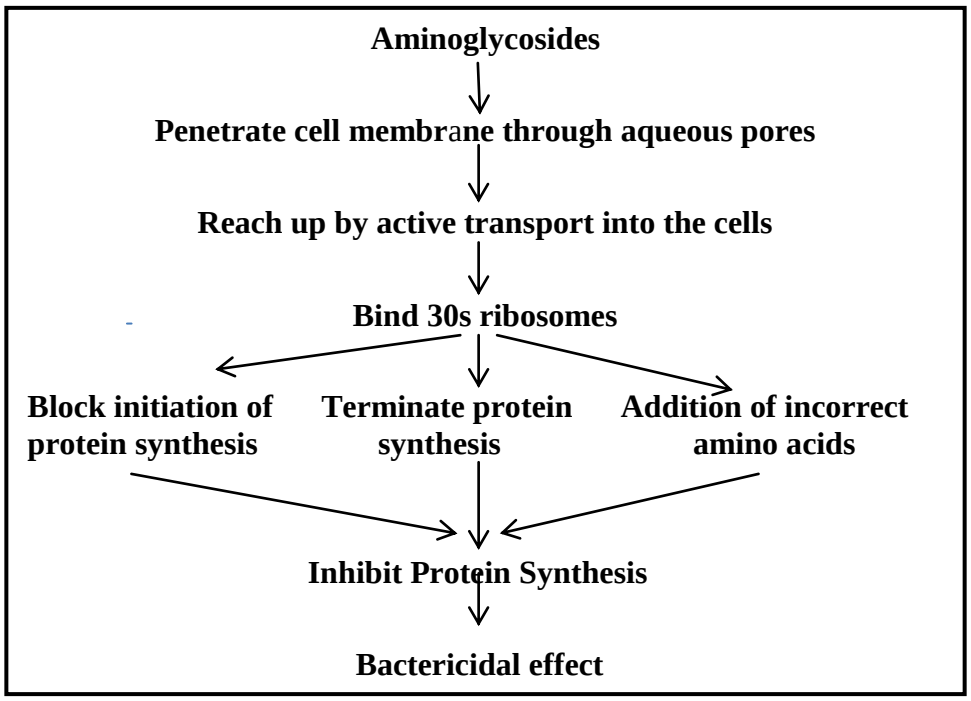

Figure No. 3: Mechanism of action of Aminoglycosides.

5. Tetracycline

In the late 1940s and early 1950s, tetracycline antibiotics were isolated from different species of Streptomyces. Since then, several semisynthetic modifications have been made to the tetracycline molecule, resulting in other tetracycline molecules with distinct pharmacokinetic characteristics and antimicrobial activities. Some of these tetracycline compounds include oxytetracycline, chlortetracycline, doxycycline, and minocycline. Chlortetracycline and oxytetracycline are natural products, while the others are semisynthetic.[17] Tetracyclines work by binding to the 30S ribosomal subunit of a susceptible organism, which interferes with the binding of aminoacyl-tRNA to the messenger RNA molecule/ribosome complex, disrupting the bacterial protein synthesis.[18] Tetracycline can also bind to the 70S ribosomes found in mitochondria and inhibit protein synthesis in mitochondria. Tetracyclines are

bacteriostatic and highly effective against multiplying bacteria. They are broad-spectrum antimicrobials and can be used to treat a wide range of Gram-positive and Gram-negative bacterial infections.[19] (As shown in figure no.4).

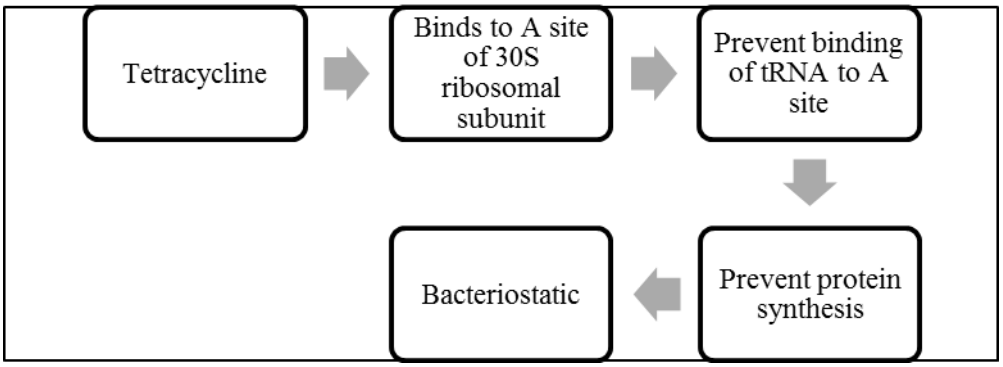

Figure No. 4: Mechanism of action of Tetracycline.

6. Sulphonamides

Sulphonamides are a group of antimicrobial compounds that have been in clinical use for fifty years. However, resistance to sulphonamides is common, which is why trimethoprim (trimethoprim-sulphonamide) or ormetoprim (ormetoprim-sulfadimethoxine) is added to broaden the spectrum and increase antibacterial activity against bacteria that would have been resistant to either drug used alone. Trimethoprim and ormetoprim are both diaminopyrimidines.

Sulphonamides are structurally similar to para-aminobenzoic acid (PABA), and their action is dependent on the chemical similarity with PABA. Sulphonamides act as a false substrate and compete with PABA for the enzyme dihydrofolate synthase, which blocks the synthesis of dihydrofolic acid (DHFA). Then, trimethoprim inhibits the synthesis of tetrahydrofolic acid (THFA), and the folate cofactor is inhibited. The folate cofactor acts as a 1-carbon donor for the synthesis of nucleic acid (DNA). As a result of blocking the biosynthesis of folate coenzyme in bacteria, the growth and division are stopped.[20] (As shown in figure no.5).

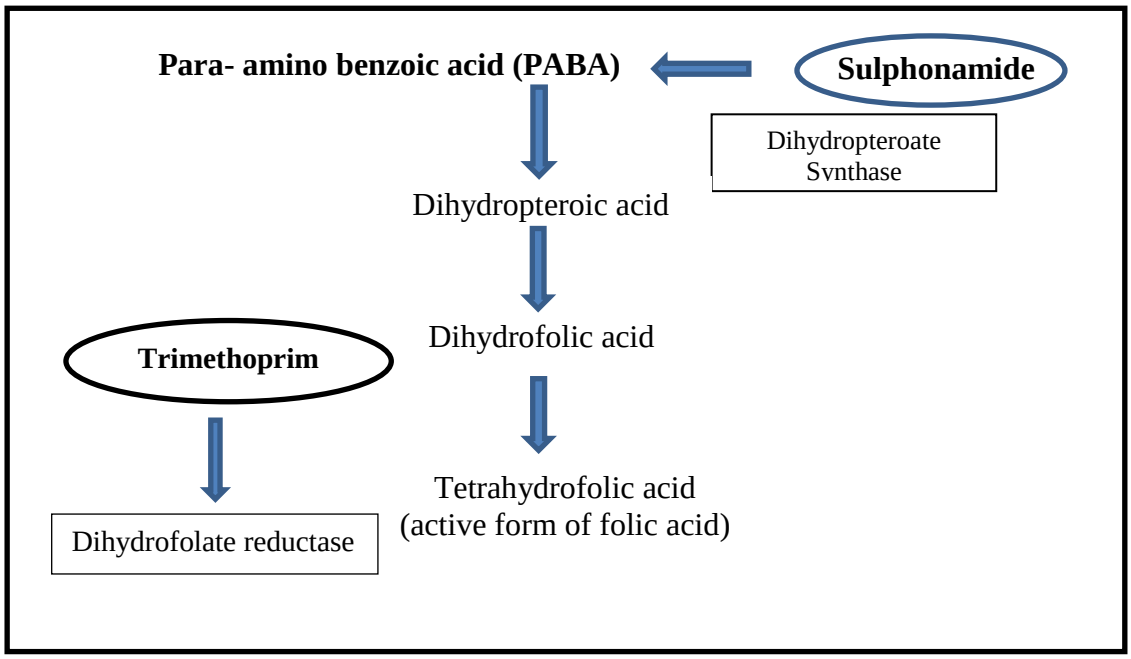

Figure No. 4: Mechanism of action of Sulphonamide.

7. Fluoroquinolones

Fluoroquinolones are synthetic antibacterial drugs that target bacterial DNA metabolism. They inhibit two enzymes: Topoisomerase II (DNA gyrase) and Topoisomerase IV. DNA gyrase introduces negative supercoils into the DNA double helix, while Topoisomerase IV plays a role in the splitting process of DNA.[21] The drugs create a bubble-shaped binding pocket in the DNA and bind to the gyrase complex, leading to permanent gaps in the DNA strands and cell death.[22] Fluoroquinolones differ in chemical substitutions but have the same core quinolone structure. They are categorized into four generations based on their antimicrobial spectrum and are 'Critically Important Antimicrobials' listed by WHO.[23] (As shown in figure no.6)

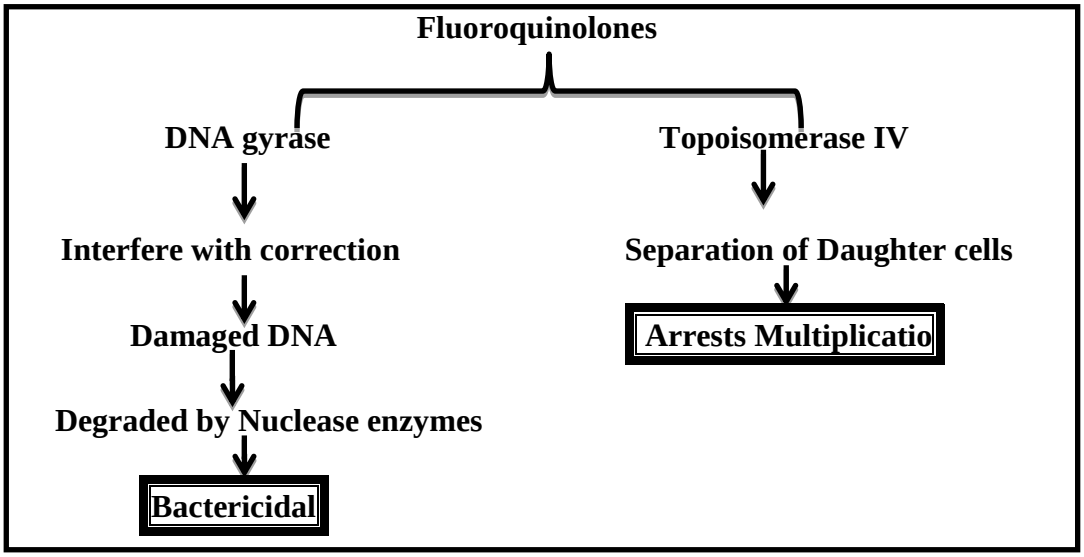

Figure No. 6: Mechanism of action of Fluoroquinolones.

Resistance to Antibiotic

Antibiotic resistance occurs when a drug loses its ability to effectively inhibit bacterial growth. Bacteria then become "resistant" and continue to multiply even in the presence of therapeutic levels of antibiotics. While antibiotics are usually effective against bacteria, the microbes can become less sensitive or resistant, requiring a higher concentration of the same drug to have an effect. Antimicrobial resistance emerged shortly after the introduction of new antimicrobial compounds. Antibiotic resistance can occur through natural selection processes, where bacteria are empowered with some degree of low-level resistance by nature. For example, sulfamethoxazole and trimethoprim (TMP-SMZ), ampicillin, and tetracycline were commonly used in the past to treat non-cholera diarrhea in Thailand but are no longer effective. However, an another study conducted in Bangladesh showed the effectiveness of the same drugs in treating the disease effectively. In fact, resistance was documented even before the beginning of antibiotic usage in fighting infections. Non-judicial use of antibiotics is responsible for making microbes resistant.

Bacteria can develop resistance to antibiotics due to their natural process. This process involves gene-level mutations, which occur in response to the selective pressure induced by antibiotics. In addition to this, bacteria can also transfer genetic material directly between each other through plasmids, meaning that resistance can evolve through mechanisms other than natural selection. Although broad spectrum antibiotics are often used to treat hospital-acquired infections, they can also contribute to the development of antibiotic resistance.[24]

Multidrug-resistant bacterial infections have high mortality rates. Every year, in the EU, approximately 25,000 patients die from these infections, and in the United States, more than 63,000 patients die from hospital-acquired bacterial infections. The economic costs of multidrug-resistant bacterial infections in the EU are staggering, with extra healthcare costs and productivity losses of at least EUR 1.5 billion per year. Treating hospital-acquired infections from six species of antibiotic-resistant bacteria alone cost at least $1.3 billion in 1992 ($1.87 billion in 2006), which is more than the annual spending on influenza.[25]

Antibiotics resistant bacterial infections

Table No. 1.

Bacteria	**Antibiotic resistant**
Gram-positive bacteria	
Staphylococcus aureus	Methicillin
Enterococcus species	Carbapenem
Streptococcus pneumoniae	beta-lactam antibiotics
Gram-negative bacteria	
Escherichia coli and Klebsiella pneumoniae	Third-generation cephalosporins
Acinetobacter baumannii	Multi-drug
Pseudomonas aeruginosa	Multidrug

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