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LIST AND EXPLAIN 4 MECHANISM OF ANTIMICROBIAL RESISTANCE.

Bacteria

Viruses

Parasite

Fungi

**Bacteria**

Antibiotic resistance through alteration of the antibiotic's target site, modeled after MRSA's resistance to penicillin. Beta-lactam antibiotics permanently inactivate [PBP enzymes](https://en.wikipedia.org/wiki/Penicillin-binding_protein), which are essential for bacterial life, by permanently binding to their active sites. [MRSA](https://en.wikipedia.org/wiki/Methicillin-resistant_Staphylococcus_aureus), however, expresses a PBP that does not allow the antibiotic into its active site.

The four main mechanisms by which bacteria exhibit resistance to antibiotics are:

1. Drug inactivation or modification: for example, enzymatic deactivation of [*penicillin* G](https://en.wikipedia.org/wiki/Penicillin) in some penicillin-resistant bacteria through the production of [β-lactamases](https://en.wikipedia.org/wiki/Beta-lactamases). Most commonly, the protective enzymes produced by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will reduce its ability to bind to the bacterial ribosomes and disrupt protein synthesis.
2. Alteration of target- or binding site: for example, alteration of [PBP](https://en.wikipedia.org/wiki/Penicillin_binding_protein)—the binding target site of penicillins—in [MRSA](https://en.wikipedia.org/wiki/Methicillin-resistant_Staphylococcus_aureus) and other penicillin-resistant bacteria. Another protective mechanism found among bacterial species is ribosomal protection proteins. These proteins protect the bacterial cell from antibiotics that target the cell's ribosomes to inhibit protein synthesis. The mechanism involves the binding of the ribosomal protection proteins to the ribosomes of the bacterial cell, which in turn changes its conformational shape. This allows the ribosomes to continue synthesizing proteins essential to the cell while preventing antibiotics from binding to the ribosome to inhibit protein synthesis.
3. Alteration of metabolic pathway: for example, some [sulfonamide](https://en.wikipedia.org/wiki/Sulfa_drugs)-resistant bacteria do not require [para-aminobenzoic acid](https://en.wikipedia.org/wiki/Para-aminobenzoic_acid) (PABA), an important precursor for the synthesis of [folic acid](https://en.wikipedia.org/wiki/Folic_acid) and [nucleic acids](https://en.wikipedia.org/wiki/Nucleic_acid) in bacteria inhibited by sulfonamides, instead, like mammalian cells, they turn to using preformed folic acid. Reduced drug accumulation: by decreasing drug [permeability](https://en.wikipedia.org/wiki/Semipermeable_membrane) or increasing active [efflux](https://en.wikipedia.org/wiki/Efflux_%28microbiology%29) (pumping out) of the drugs across the cell surface These pumps within the cellular membrane of certain bacterial species are used to pump antibiotics out of the cell before they are able to do any damage. They are often activated by a specific substrate associated with an antibiotic. as in [fluoroquinolone](https://en.wikipedia.org/wiki/Fluoroquinolone) resistance.
4. Ribosome splitting and recycling: for example, drug-mediated stalling of the ribosome by [lincomycin](https://en.wikipedia.org/wiki/Lincomycin%22%20%5Co%20%22Lincomycin) and [erythromycin](https://en.wikipedia.org/wiki/Erythromycin) unstalled by a heat shock protein found in *Listeria monocytogenes*, which is an homologous of HflX from other bacteria. Liberation of the ribosome from the drug allows further translation and consequent resistance to the drug. 

A number of mechanisms used by common antibiotics to deal with bacteria and ways by which bacteria become resistant to them.

In gram-negative bacteria, plasmid-mediated resistance genes produce proteins that can bind to [DNA gyrase](https://en.wikipedia.org/wiki/DNA_gyrase), protecting it from the action of quinolones. Finally, mutations at key sites in DNA gyrase or [topoisomerase IV](https://en.wikipedia.org/wiki/Topoisomerase_IV) can decrease their binding affinity to quinolones, decreasing the drug's effectiveness. Some bacteria are naturally resistant to certain antibiotics; for example, gram-negative bacteria are resistant to most [β-lactam antibiotics](https://en.wikipedia.org/wiki/%CE%92-lactam_antibiotic) due to the presence of [β-lactamase](https://en.wikipedia.org/wiki/Beta-lactamases). Antibiotic resistance can also be acquired as a result of either genetic mutation or [horizontal gene transfer](https://en.wikipedia.org/wiki/Horizontal_gene_transfer). Although mutations are rare, with spontaneous mutations in the [pathogen](https://en.wikipedia.org/wiki/Pathogen) [genome](https://en.wikipedia.org/wiki/Genome) occurring at a rate of about 1 in 105 to 1 in 108 per chromosomal replication, the fact that bacteria reproduce at a high rate allows for the effect to be significant. Given that lifespans and production of new generations can be on a timescale of mere hours, a new (de novo) mutation in a parent cell can quickly become an [inherited](https://en.wikipedia.org/wiki/Heredity) mutation of widespread prevalence, resulting in the [microevolution](https://en.wikipedia.org/wiki/Microevolution) of a fully resistant colony. However, chromosomal mutations also confer a cost of fitness. For example, a ribosomal mutation may protect a bacterial cell by changing the binding site of an antibiotic but will also slow protein synthesis. manifesting, in slower growth rate. Moreover, some adaptive mutations can propagate not only through inheritance but also through [horizontal gene transfer](https://en.wikipedia.org/wiki/Horizontal_gene_transfer). The most common mechanism of horizontal gene transfer is the transferring of [plasmids](https://en.wikipedia.org/wiki/Plasmid-mediated_resistance) carrying antibiotic resistance genes between bacteria of the same or different species via [conjugation](https://en.wikipedia.org/wiki/Bacterial_conjugation). However, bacteria can also acquire resistance through [transformation](https://en.wikipedia.org/wiki/Transformation_%28genetics%29), as in *Streptococcus pneumoniae* uptaking of naked fragments of extracellular DNA that contain antibiotic resistance genes to streptomycin, through [transduction](https://en.wikipedia.org/wiki/Transduction_%28genetics%29), as in the bacteriophage-mediated transfer of tetracycline resistance genes between strains of *S. pyogenes*, [or through [gene transfer agents](https://en.wikipedia.org/wiki/Gene_transfer_agent), which are particles produced by the host cell that resemble bacteriophage structures and are capable of transferring DNA

[] Antibiotic resistance can be introduced artificially into a microorganism through laboratory protocols, sometimes used as a [selectable marker](https://en.wikipedia.org/wiki/Selectable_marker) to examine the mechanisms of gene transfer or to identify individuals that absorbed a piece of DNA that included the resistance gene and another gene of interest.

 Recent findings show no necessity of large populations of bacteria for the appearance of antibiotic resistance. Small populations of *E. coli* in an antibiotic gradient can become resistant. Any heterogeneous environment with respect to nutrient and antibiotic gradients may facilitate antibiotic resistance in small bacterial populations. Researchers hypothesize that the mechanism of resistance development is based on four SNP mutations in the genome of *E. coli* produced by the gradient of antibiotic.

In recent years, the emergence and spread of [β-lactamases](https://en.wikipedia.org/wiki/Beta-lactamases) called [carbapenemases](https://en.wikipedia.org/wiki/Carbapenemase%22%20%5Co%20%22Carbapenemase) has become a major health crisis. One such carbapenemase is [New Delhi metallo-beta-lactamase 1](https://en.wikipedia.org/wiki/New_Delhi_metallo-beta-lactamase_1) (NDM-1), an [enzyme](https://en.wikipedia.org/wiki/Enzyme) that makes [bacteria](https://en.wikipedia.org/wiki/Bacteria) [resistant](https://en.wikipedia.org/wiki/Antibiotic_resistance) to a broad range of [beta-lactam antibiotics](https://en.wikipedia.org/wiki/Beta-lactam_antibiotic). The most common bacteria that make this enzyme are [gram-negative](https://en.wikipedia.org/wiki/Gram-negative_bacteria) such as [*Escherichia coli*](https://en.wikipedia.org/wiki/Escherichia_coli) and *Klebsiella pneumoniae*, but the gene for NDM-1 can spread from one strain of bacteria to another by [horizontal gene transfer](https://en.wikipedia.org/wiki/Horizontal_gene_transfer).

**Viruses**

Specific [antiviral drugs](https://en.wikipedia.org/wiki/Antiviral_drug) are used to treat some viral infections. These drugs prevent viruses from reproducing by inhibiting essential stages of the virus's replication cycle in infected cells. Antivirals are used to treat [HIV](https://en.wikipedia.org/wiki/HIV), [hepatitis B](https://en.wikipedia.org/wiki/Hepatitis_B), [hepatitis C](https://en.wikipedia.org/wiki/Hepatitis_C), [influenza](https://en.wikipedia.org/wiki/Influenza), [herpes viruses](https://en.wikipedia.org/wiki/Herpesviridae) including [varicella zoster virus](https://en.wikipedia.org/wiki/Varicella_zoster_virus), [cytomegalovirus](https://en.wikipedia.org/wiki/Cytomegalovirus) and [Epstein-Barr virus](https://en.wikipedia.org/wiki/Epstein-Barr_virus). With each virus, some strains have become resistant to the administered drugs.

 Antiviral drugs typically target key components of viral reproduction; for example, [oseltamivir](https://en.wikipedia.org/wiki/Oseltamivir%22%20%5Co%20%22Oseltamivir) targets influenza [neuraminidase](https://en.wikipedia.org/wiki/Neuraminidase), while guanosine analogs inhibit viral DNA polymerase. Resistance to antivirals is thus acquired through mutations in the genes that encode the protein targets of the drugs.

Resistance to HIV antivirals is problematic, and even multi-drug resistant strains have evolved. One source of resistance is that many current HIV drugs, including NRTIs and NNRTIs, target [reverse transcriptase](https://en.wikipedia.org/wiki/Reverse_transcriptase); however, HIV-1 reverse transcriptase is highly error prone and thus mutations conferring resistance arise rapidly.  Resistant strains of the HIV virus emerge rapidly if only one antiviral drug is used. Using three or more drugs together, termed [combination therapy](https://en.wikipedia.org/wiki/Combination_therapy), has helped to control this problem, but new drugs are needed because of the continuing emergence of drug-resistant HIV strains.

**Fungi**

Infections by fungi are a cause of high morbidity and mortality in [immunocompromised](https://en.wikipedia.org/wiki/Immunodeficiency) persons, such as those with HIV/AIDS, tuberculosis or receiving [chemotherapy](https://en.wikipedia.org/wiki/Chemotherapy). The fungi [candida](https://en.wikipedia.org/wiki/Candida_%28fungus%29), [*Cryptococcus neoformans*](https://en.wikipedia.org/wiki/Cryptococcus_neoformans) and [*Aspergillus fumigatus*](https://en.wikipedia.org/wiki/Aspergillus_fumigatus) cause most of these infections and antifungal resistance occurs in all of them.  Multidrug resistance in fungi is increasing because of the widespread use of antifungal drugs to treat infections in immunocompromised individuals.

Of particular note, [Fluconazole](https://en.wikipedia.org/wiki/Fluconazole)-resistant Candida species have been highlighted as a growing problem by the CDC.[[]](https://en.wikipedia.org/wiki/Antimicrobial_resistance#cite_note-CDC2013-37) More than 20 species of Candida can cause [Candidiasis](https://en.wikipedia.org/wiki/Candidiasis) infection, the most common of which is [*Candida albicans*](https://en.wikipedia.org/wiki/Candida_albicans). Candida yeasts normally inhabit the skin and mucous membranes without causing infection. However, overgrowth of Candida can lead to Candidiasis. Some Candida strains are becoming resistant to first-line and second-line [antifungal agents](https://en.wikipedia.org/wiki/Antifungal) such as [azoles](https://en.wikipedia.org/wiki/Azole#Use_as_anti-fungal_agents) and [echinocandins](https://en.wikipedia.org/wiki/Echinocandin%22%20%5Co%20%22Echinocandin).

**Parasites**

The [protozoan](https://en.wikipedia.org/wiki/Protozoa) parasites that cause the diseases [malaria](https://en.wikipedia.org/wiki/Malaria), [trypanosomiasis](https://en.wikipedia.org/wiki/Trypanosomiasis), [toxoplasmosis](https://en.wikipedia.org/wiki/Toxoplasmosis), [cryptosporidiosis](https://en.wikipedia.org/wiki/Cryptosporidiosis) and [leishmaniasis](https://en.wikipedia.org/wiki/Leishmaniasis) are important human pathogens.

Malarial parasites that are resistant to the drugs that are currently available to infections are common and this has led to increased efforts to develop new drugs.  Resistance to recently developed drugs such as [artemisinin](https://en.wikipedia.org/wiki/Artemisinin%22%20%5Co%20%22Artemisinin) has also been reported. The problem of drug resistance in malaria has driven efforts to develop vaccines.

 [Trypanosomes](https://en.wikipedia.org/wiki/Trypanosoma) are parasitic protozoa that cause [African trypanosomiasis](https://en.wikipedia.org/wiki/African_trypanosomiasis) and [Chagas disease](https://en.wikipedia.org/wiki/Chagas_disease) (American trypanosomiasis). There are no vaccines to prevent these infections so drugs such as [pentamidine](https://en.wikipedia.org/wiki/Pentamidine%22%20%5Co%20%22Pentamidine) and [suramin](https://en.wikipedia.org/wiki/Suramin%22%20%5Co%20%22Suramin), [benznidazole](https://en.wikipedia.org/wiki/Benznidazole%22%20%5Co%20%22Benznidazole) and [nifurtimox](https://en.wikipedia.org/wiki/Nifurtimox%22%20%5Co%20%22Nifurtimox) are used to treat infections. These drugs are effective but infections caused by resistant parasites have been reported.

 [Leishmaniasis](https://en.wikipedia.org/wiki/Leishmaniasis) is caused by protozoa and is an important public health problem worldwide, especially in sub-tropical and tropical countries. Drug resistance has "become a major concern".