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Antibiotics

Antibiotics or **antibacterials**

Are a type of antimicrobial used in the treatment and prevention of bacterial infection. They may either kill or inhibit the growth of bacteria. Several antibiotics are also effective against fungi and protozoans, and some are toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately.

Antibiotic (**New** definition):

> Substance produced by a microorganism or a similar product produced wholly (**synthetic**) or partially (**semi-synthetic**) by chemical synthesis and in low concentrations inhibits the growth of or kills microorganisms

In 1929, Alexander Fleming identified penicillin, the first chemical compound with antibiotic properties. Fleming was working on a culture of disease-causing bacteria when he noticed the spores of little green mold in one of his culture plates. He observed that the presence of the mold killed or prevented the growth of the bacteria.

Antibiotics revolutionized medicine in the 20th century, and have together with vaccination led to the near eradication of diseases such astuberculosis in the developed world. Their effectiveness and easy access led to overuse, especially in live-stock raising, prompting bacteria to develop resistance. This has led to widespread problems with antimicrobial and antibiotic resistance, so much as to prompt the World Health Organization to classify antimicrobial resistance as a "serious threat [that] is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country

The era of antibacterial chemotherapy began with the discovery of arsphenamine, first synthesized by Alfred Bertheim and Paul Ehrlich in 1907, used to treat syphilis. The first systemically active antibacterial drug, prontosil was discovered in 1933 by Gerhard Domagk, for which he was awarded the 1939 Nobel Prize. All classes of antibiotics in use today were first discovered prior to the mid 1980s.

Sometimes the term antibiotic is used to refer to any substance used against microbes,[9] synonymous to antimicrobial. Some sources distinguish between antibacterial and antibiotic; antibacterials used in soaps and cleaners etc., but not as medicine. This article treats the terms as synonymous and according to the most widespread definition of antibiotics being a substance used against bacteria.

Although there are a number of different types of antibiotic they all work in one of two ways:

- A **bactericidal** antibiotic kills the bacteria. Penicillin is a bactericidal. A bactericidal usually either interferes with the formation of the bacterium's cell wall or its cell contents.
- A **bacteriostatic** stops bacteria from multiplying.

Medical uses

Treatment

- Bacterial infection
- Protozoan infection, e.g., metronidazole and Bactrim is effective against several parasitics

- Immunomodulation, e.g., tetracycline, which is effective in periodontal inflammation, and dapsone, which is effective in autoimmune diseases such as oral mucous membrane
- pemphigoid
- Nonoperative resource for patients who have non-complicated acute appendicitis. Treatment with antibiotics has been reported to work, with almost no cases of remission.
- Prevention of infection
  - Surgical wound
  - DentalantibioticprophylaxisConditions of neutropenia, e.g. cancer-related

Pharmacodynamics

The successful outcome of antimicrobial therapy with antibacterial compounds depends on several factors. These include host defense mechanisms, the location of infection, and the pharmacokinetic and pharmacodynamic properties of the antibacterial.[16] A bactericidal activity of antibacterials may depend on the bacterial growth phase, and it often requires ongoing metabolic activity and division of bacterial cells.[17] These findings are based on laboratory studies, and in clinical settings have also been shown to eliminate bacterial infection.[16][18] Since

the activity of antibacterials depends frequently on its concentration,[19] *in vitro* characterization of antibacterial activity commonly includes the determination of the minimum inhibitory concentration and minimum bactericidal concentration of an antibacterial. To predict clinical outcome, the antimicrobial activity of an antibacterial is usually combined with its pharmacokinetic profile, and several pharmacological parameters are used as markers of drug efficacy.

Classes

Antibacterial antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity. Most target bacterial functions or growth processes. Those that target the bacterial cell wall (penicillins and cephalosporins) or the cell membrane (polymyxins), or interfere with essential bacterial enzymes (rifamycins, lipiarmycins, quinolones,and sulfonamides)
have bactericidal activities. Those that target protein synthesis (macrolides, lincosamides and tetracyclines)areusually bacteriostatic (withtheexceptionof bactericidal aminoglycosides). Further categorization is based on their target specificity. "Narrow-spectrum" antibacterial antibiotics target specific types of bacteria, such as Gram-negative or Gram-positive bacteria, whereas broad-spectrum antibiotics affect a wide range of bacteria. Following a 40-year hiatus in discovering new classes of antibacterial compounds, four new classes of antibacterial antibiotics have been brought into clinical use in the late 2000s and early 2010s:
cyclic lipopeptides (suchas daptomycin), glycylcyclines (suchastigecycline),oxazolidinones (suchas linezolid),and lipiarmycins (suchasfidaxomicin).

Production

With advances in medicinal chemistry, most modern antibacterials are semisynthetic modifications of various natural compounds.[26] These include, for example, the beta-lactam antibiotics, which include the penicillins (produced by fungi in the genus *Penicillium*), the cephalosporins, and the carbapenems. Compounds that are still isolated from living organisms are the aminoglycosides, whereas other antibacterials—for example, the sulfonamides, the quinolones, and the oxazolidinones—are produced solely by chemical synthesis. In accordance with this, many antibacterial compounds are classified on the basis of chemical/biosynthetic origin into natural, semisynthetic, and synthetic. Another classification system is based on biological activity; in this classification, antibacterials are divided into two broad groups

according to their biological effect on microorganisms:Bactericidal agents kill bacteria, and bacteriostatic agents slow down or stall bacterial growthMany antibacterial compounds are relatively small molecules with amolecular weight of less than 2000 atomic mass units

Since the first pioneering efforts of Florey and Chain in 1939, the importance of antibiotics, including antibacterials, to medicine has led to intense research into producing antibacterials at large scales. Following screening of antibacterials against a wide range of bacteria, production of the active compounds is carried out using fermentation, usually in strongly aerobic conditions.

Administration

Oral antibiotics are taken by mouth, whereas intravenous administration may be used in more serious casessuch as deep-seated systemic infections. Antibiotics may also sometimes be administered topically, as with eye drops or ointments.

The topical antibiotics are: Erythromycin

- Clindamycin
- Gentamycin
- Tetracycline
- Meclocycline
- (Sodium) sulfacetamide

While topical medications that act as Comedolytics as well as antibiotics are:

- Benzoyl peroxide
- Azelaic acid

Side-effects

Antibiotics are screened for any negative effects on humans or other mammals before approval for clinical use, and are usually considered safe and most are well-tolerated. However, some antibiotics have been associated with a range of adverse side effects. Side-effects range from mild to very serious depending on the antibiotics used, the microbial organisms targeted, and the individual patientSafety profiles of newer drugs are often not as well-established as for those that have a long history of use. Adverse effects range from fever and nausea to major allergic reactions, including photodermatitis and anaphylaxis Common

side-effects include diarrhea, resulting from disruption of the species composition in the intestinal flora, resulting, for example, in overgrowth of pathogenic bacteria, such as *Clostridium difficile*. Antibacterials can also affect the vaginal flora, and may lead to overgrowth of yeast species of the genus *Candida* in the vulvo-vaginal area.[31] Additional side-effects can result from interaction with other drugs, such as elevated risk of tendon damage from administration of a quinolone antibiotic with a systemic corticosteroid. Some scientists have hypothesized that the indiscriminate use of antibiotics alter the host microbiota and this has been associated with chronic disease

Drug-drug interactions

Birth control pills

The majority of studies indicate antibiotics do not interfere with contraceptive pills, such as clinical studies that suggest the failure rate of contraceptive pills caused by antibiotics is very low (about 1%). In cases where antibacterials have been suggested to affect the efficiency of birth control pills, such as for the broad-spectrum antibacterial rifampicin, these cases may be due to an increase in the activities of hepatic liver enzymes' causing increased breakdown of the pill's active ingredients. Effects on the intestinal flora, which might result in reduced absorption of estrogens in the colon, have also been suggested, but such suggestions have been inconclusive and controversial. Clinicians have recommended that extra contraceptive measures be applied during therapies using antibacterials that are suspected to interact with oral contraceptives.

Alcohol

Interactions between alcohol and certain antibiotics may occur and may cause side-effects and decreased effectiveness of antibiotic therapy.[38][39]

> "It is sensible to avoid drinking alcohol when taking medication. However, it is unlikely that drinking alcohol in moderation will cause problems if you are taking most common antibiotics. However, there are specific types of antibiotics with which alcohol should be avoided completely, because of serious side-effects."[1]

Therefore, potential risks of side-effects and effectiveness depend on the type of antibiotic administered. Despite the lack of a categorical counterindication, the belief that alcohol and antibiotics should never be mixed is widespread.

Antibioticssuchas metronidazole, tinidazole, cephamandole, latamoxef, cefoperazone, cefmenoxime, and furazolidone, cause a disulfiram-

like chemical reaction with alcohol by inhibiting its breakdown by acetaldehyde dehydrogenase, which may result in vomiting, nausea, and shortness of breath.

Other effects of alcohol on antibiotic activity include altered activity of the liver enzymes that break down the antibiotic compound. In addition, serum levels of doxycycline anderythromycin succinate] two bacteriostatic antibiotics (see above) may be reduced by alcohol consumption, resulting in reduced efficacy and diminished pharmacotherapeutic effect.

Resistance

The emergence of resistance of bacteria to antibiotics is a common phenomenon.Emergenceofresistanceoftenreflectsevolutionary processes that take place during antibiotic therapy. The antibiotic treatment may select for bacterial strains with physiologically or genetically enhanced capacity to survive high doses of antibiotics. Under certain conditions, it may result in preferential growth of resistant bacteria, while growth of susceptible bacteria is inhibited by the drug.[42] For example, antibacterial selection for strains having previously acquired antibacterial-resistance genes was demonstrated in 1943 by the Luria–Delbrück experiment. Antibiotics such as penicillin and erythromycin, which used to have a high efficacy against many bacterial species and strains, have become less effective, due to the increased resistance of many bacterial strains.

Resistance may take the form of biodegredation of pharmaceuticals, such as sulfamethazine-degrading soil bacteria introduced to sulfamethazine through medicated pig feces. The survival of bacteria often results from an inheritable resistance, but the growth of resistance to antibacterials also occurs through horizontal gene transfer. Horizontal transfer is more likely to happen in locations of frequent antibiotic use.

Antibacterial resistance may impose a biological cost, thereby reducing fitness of resistant strains, which can limit the spread of antibacterial-resistant bacteria, for example, in the absence of antibacterial compounds. Additional mutations, however, may compensate for this fitness cost and can aid the survival of these bacteria.

Paleontological data show that both antibiotics and antibiotic resistance are ancient compounds and mechanisms. Useful antibiotic targets are those for which mutations negatively impact bacterial reproduction or viability.

Several molecular mechanisms of antibacterial resistance exist. Intrinsic antibacterial resistance may be part of the genetic makeup of bacterial strains. For example, an antibiotic target may be absent from the bacterial genome. Acquired resistance results from a mutation in the bacterial chromosome or the acquisition of extra-chromosomal DNA. Antibacterial-producing bacteria have evolved resistance mechanisms that have been shown to be similar to, and may have been transferred to, antibacterial-resistant strains. The spread of antibacterial resistance often occurs through vertical transmission of mutations during growth and by genetic recombination of DNA by horizontal genetic exchange. For instance, antibacterial resistance genes can be exchanged between different bacterial strains or species via plasmids that carry these resistance genes. Plasmids that carry several different resistance genes can confer resistance to multiple antibacterials Cross-resistance to several antibacterials may also occur when a resistance mechanism encoded by a single gene conveys resistance to more than one antibacterial compound.

Antibacterial-resistant strains and species, sometimes referred to as "superbugs", now contribute to the emergence of diseases that were for a while well-controlled. For example, emergent bacterial strains causing tuberculosis (TB) that are resistant to previously effective antibacterial treatments pose many therapeutic challenges. Every year, nearly half a million new cases of multidrug-resistant tuberculosis (MDR-TB) are estimated to occur worldwide.[55] For example, NDM-1 is a newly identified enzyme conveying bacterial resistance to a broad range of beta-lactam antibacterials.[56] The United Kingdom's Health Protection Agency has stated that "most isolates with NDM-1 enzyme are resistant to all standard intravenous antibiotics for treatment of severe infections."

Misuse

Inappropriate antibiotic treatment and overuse of antibiotics have contributed to the emergence of antibiotic-resistant bacteria. Self prescription of antibiotics is an example of misuse. Many antibiotics are frequently prescribed to treat symptoms or diseases that do not respond to antibiotics or that are likely to resolve without treatment. Also, incorrect or suboptimal antibiotics are prescribed for certain bacterial infections. The overuse of antibiotics, like penicillin and erythromycin, has been associated with emerging antibiotic resistance since the 1950s Widespread usage of antibiotics in hospitals has also been associated with increases in bacterial strains and species that no longer respond to treatment with the most common antibiotics.

Common forms of antibiotic misuse include excessive use of prophylactic antibiotics in travelers and failure of medical professionals to prescribe the correct dosage of antibiotics on the basis of the patient's weight and history of prior use. Other forms of misuse include failure to take the entire prescribed course of the antibiotic, incorrect dosage and administration, or failure to rest for sufficient recovery. Inappropriate antibiotic treatment, for example, is their prescription to treat viral infections such as the common cold. One study onrespiratory tract infections found "physicians were more likely to prescribe antibiotics to patients who appeared to expect them".[61]Multifactorial interventions aimed at both physicians and patients can reduce inappropriate prescription of antibiotics.

Several organizations concerned with antimicrobial resistance are lobbying to eliminate the unnecessary use of antibiotics.[59] The issues of misuse and overuse of antibiotics have been addressed by the formation of the US Interagency Task Force on Antimicrobial Resistance. This task force aims to actively address antimicrobial resistance, and is coordinated by the US Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), as well as other US agencies. An NGO campaign group is *Keep Antibiotics Working*. In France, an "Antibiotics are not automatic" government campaign started in 2002 and led to a marked reduction of unnecessary antibiotic prescriptions, especially in children.

The emergence of antibiotic resistance has prompted restrictions on their use in the UK in 1970 (Swann report 1969), and the EU has banned the use of antibiotics as growth-promotional agents since 2003.[66] Moreover, several organizations (e.g., The American Society for Microbiology (ASM), American Public Health Association (APHA) and the American Medical Association (AMA)) have called for restrictions on antibiotic use in food animal production and an end to all nontherapeutic uses .However, commonly there are delays in regulatory and legislative actions to limit the use of antibiotics, attributable partly to resistance against such regulation by industries using or selling antibiotics, and to the time required for research to test causal links between their use and resistance to them. Two federal bills (S.742 and H.R. 2562) aimed at phasing out nontherapeutic use of antibiotics in US food animals were proposed, but have not passed These bills were endorsed by public health and medical organizations, including the American Holistic Nurses' Association, the American Medical Association, and the American Public Health Association (APHA).

There has been extensive use of antibiotics in animal husbandry. In the United States, the question of emergence of antibiotic-resistant bacterial strains due to use of antibiotics in livestock was raised by the US Food and Drug Administration (FDA) in 1977. In March 2012, the United States District Court for the Southern District of New York, ruling in an action brought by the Natural Resources Defense Council and others, ordered the FDA to revoke approvals for the use of antibiotics in livestock, which violated FDA regulations.

Alternatives

The increase in bacterial strains that are resistant to conventional antibacterial therapies has prompted the development of bacterial disease treatment strategies that are alternatives to conventional antibacterials.

Resistance-modifying agents

One strategy to address bacterial drug resistance is the discovery and application of compounds that modify resistance to common antibacterials. For example, some resistance-modifying agents may inhibit multidrug resistance mechanisms, such as drug efflux from the cell, thus increasing the susceptibility of bacteria to an antibacterial. Targets include:

- The efflux inhibitor Phe-Arg-β-naphthylamide.
- Beta-lactamase inhibitors, such as clavulanic acid and sulbactam.

Metabolic stimuli such as sugar can help eradicate a certain type of antibiotic-tolerant bacteria by keeping their metabolism active.

Vaccines

Vaccines rely on immune modulation or augmentation. Vaccination either excites or reinforces the immune competence of a host to ward off infection, leading to the activation ofmacrophages, the production of antibodies, inflammation, and other classic immune reactions. Antibacterial vaccines have been responsible for a drastic reduction in global bacterial diseases. Vaccines made from attenuated whole cells or lysates have been replaced largely by less reactogenic, cell-free vaccines consisting of purified components, including capsular polysaccharides and their conjugates, to protein carriers, as well as inactivated toxins (toxoids) and proteins.

Phage therapy

Phage therapy is another option that is being looked into for treating resistant strains of bacteria. The way that researchers are doing this is

by infecting pathogenic bacteria with their own viruses, more specifically, bacteriophages. Bacteriophages, also known simply as phages, are precisely bacterial viruses that infect bacteria by disrupting pathogenic bacterium lytic cycles.[1] By disrupting the lytic cycles of bacterium, phages destroy their metabolism, which eventually results in the cell's death Phages will insert their DNA into the bacterium, allowing their DNA to be transcribed. Once their DNA is transcribed the cell will proceed to make new phages and as soon as they are ready to be released, the cell will lyse . One of the worries about using phages to fight pathogens is that the phages will infect "good" bacteria, or the bacteria that are important in the everyday function of human beings. However, studies have proven that phages are very specific when they target bacteria, which makes researchers confident that bacteriophage therapy is the definite route to defeating antibiotic resistant bacteria.

Supplements

Someover-the-counter antioxidant supplementscontaining polyphenols, such as grape seed extract, demonstrate *in vitro* anti-bacterial properties.

Status of new antibiotics development

In a policy report released by the Infectious Disease Society of America (IDSA) on April 2013, IDSA expressed grave concern over the weak pipeline of antibiotics to combat the growing ability of bacteria, especially the Gram-negative bacilli (GNB), to develop resistance to antibiotics. Since 2009, only 2 new antibiotics were approved in United States, and the number of new antibiotics annually approved for marketing continues to decline. The report could identify only seven antibiotics currently in phase 2 or phase 3 clinical trials to treat the GNB, which includes *E. coli*, *Salmonella*, *Shigella*, and the *Enterobacteriaceae* bacteria, and these drugs do not address the entire spectrum of the resistance developed by those bacteria. Some of these seven new antibiotics are combination of existent antibiotics, including:

- Ceftolozane/tazobactam (CXA-201;CXA-101/tazobactam): Antipseudomonal cephalosporin/β-lactamase inhibitor combination (cell wall synthesis inhibitor). FDA approved on 12/19/2014.
- Ceftazidime/avibactam (ceftazidime/NXL104): Antipseudomonal cephalosporin/β-lactamase inhibitor combination (cell wall synthesis inhibitor). In phase 3.

- Ceftaroline/avibactam (CPT-avibactam; ceftaroline/NXL104): Anti-MRSA cephalosporin/ β-lactamase inhibitor combination (cell wall synthesis inhibitor)
- Imipenem/MK-7655: Carbapenem/ β-lactamase inhibitor combination (cell wall synthesis inhibitor). In phase 2.
- Plazomicin (ACHN-490): Aminoglycoside (protein synthesis inhibitor). In phase 2.
- Eravacycline (TP-434): A synthetic tetracycline derivative / protein synthesis inhibitor targeting the ribosome being developed by Tetraphase. Phase 2 trials complete.[81]
- Brilacidin (PMX-30063): Peptide defense protein mimetic (cell membrane disruption). In phase 2.

Many new antibiotics are still to come from research into *Streptomyces*, including new pharmaceuticals able to treat MRSA and other infections resistant to commonly-used medication. Investments into this sector of research have made a profound impact on the UK economy and human health. *Streptomyces* research supported by BBSRC at theJohn Innes Centre and universities in the UK has resulted in the creation of a number of spin-out companies. One of them, Novacta Biosystems, has designed the type-b lantibiotic-based compound NVB302 (in phase 1) to treat *Clostridium difficile* infections.

The IDSA's prognosis for sustainable R&D infrastructure for antibiotics development will depend upon clarification of FDA regulatory clinical trial guidance that would facilitate the speedy approval of new drugs, and the appropriate economic incentives for the pharmaceuticals companies to invest in this endeavor.[80] On 12 December 2013, the Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013 was introduced in the US Congress. The ADAPT Act aims to fast track the drug development in order to combat the growing public health threat of 'superbugs'. Under this Act, FDA can approve antibiotics and antifungals needed for life-threatening infections based on data from smaller clinical trials. The CDC will reinforce the monitoring of the use of antibiotics that treat serious and life-threatening infections and the emerging resistance, and make the data publicly available. The FDA antibiotics labeling process, 'Susceptibility Test Interpretive Criteria for Microbial Organisms' or 'breakpoints' is also streamlined to allow the most up-to-date and cutting-edge data available to healthcare professionals under the new Act.[84][85] Congress has been urged in 2014 from several parties to aid the development of new drugs via bills such as ADAPT. Allan Coukell, director of drugs and medical

devices at The Pew Charitable Trusts, testified in from of the House Committee, in a statement published by Reuters, that "By allowing drug developers to rely on smaller datasets, and clarifying FDA's authority to tolerate a higher level of uncertainty for these drugs when making a risk/benefit calculation, ADAPT would make the clinical trials more feasible."[86]

Antibiotics antagonism

Chloramphenicol and tetracyclines areantagoniststo penicillins and aminoglycosides. This means the combined effect of two antibiotics from separate groups can be less than a single antibiotic. However, this can vary depending on the species of bacteria.[87]

Five Basic Mechanisms of Antibiotic Action against Bacterial Cells:

1. Inhibition of Cell Wall Synthesis (most common mechanism)
2. Inhibition of Protein Synthesis (Translation) (second largest class)
3. Alteration of Cell Membranes
4. Inhibition of Nucleic Acid Synthesis
5. Antimetabolite Activity

Inhibition of Cell Wall Synthesis

Beta-Lactams ---> Inhibition of peptidoglycan synthesis (bactericidal)

Resistance --->

(1) fails to cross membrane (gram negatives)

(2) fails to bind to altered PBP’s

(3) hydrolysis by beta-lactamases

Vancomycin ---> Disrupts peptidoglycan cross-linkage

Resistance --->

(1) fails to cross gram negative outer membrane (too large)

(2) some intrinsically resistant (pentapeptide terminus)

Bacitracin ---> Disrupts movement of peptidoglycan precursors (topical use)

Resistance ---> fails to penetrate into cell

Antimycobacterial agents ---> Disrupt mycolic acid or arabinoglycan synthesis (bactericidal)

Resistance --->

(1) reduced uptake

(2) alteration of target sites

Inhibition of Protein Synthesis (Translation)

30S Ribosome site

Aminoglycosides ---> Irreversibly bind 30S ribosomal proteins (bactericidal)

Resistance --->

(1) mutation of ribosomal binding site

(2) decreased uptake

(3) enzymatic modification of antibiotic

Tetracyclines ---> Block tRNA binding to 30S ribosome-mRNA complex (b-static)

Resistance --->

(1) decreased penetration

(2) active efflux of antibiotic out of cell

(3) protection of 30S ribosome

50S Ribosome site

Chloramphenicol ---> Binds peptidyl transferase component of 50S ribosome, blocking peptide elongation (bacteriostatic)

Resistance --->

(1) plasmid-encoded chloramphenicol transferase

(2) altered outer membrane (chromosomal mutations)

Macrolides ---> Reversibly bind 50S ribosome, block peptide elongation (b-static)

Resistance --->

(1) methylation of 23S ribosomal RNA subunit

(2) enzymatic cleavage (erythromycin esterase)

(3) active efflux

Clindamycin ---> Binds 50S ribosome, blocks peptide elongation; Inhibits peptidyl transferase by interfering with binding of amino acid-acyl-tRNA complex

Resistance ---> methylation of 23S ribosomal RNA subunit

Alteration of Cell Membranes

Polymyxins (topical) ---> Cationic detergent-like activity (topical use)

Resistance ---> inability to penetrate outer membrane

Bacitracin (topical) ---> Disrupt cytoplasmic membranes

Resistance ---> inability to penetrate outer membrane

Inhibition of Nucleic Acid Synthesis

- DNA Effects

Quinolones ---> Inhibit DNA gyrases or topoisomerases required for supercoiling of DNA; bind to alpha subunit

Resistance --->

(1) alteration of alpha subunit of DNA gyrase (chromosomal)

(2) decreased uptake by alteration of porins (chromosomal)

Metronidazole ---> Metabolic cytotoxic byproducts disrupt DNA

Resistance --->

(1) decreased uptake

(2) elimination of toxic compounds before they interact

RNA Effects (Transcription)

Rifampin ---> Binds to DNA-dependent RNA polymerase inhibiting initiation & Rifabutin of RNA synthesis

Resistance --->

(1) altered of beta subunit of RNA polymerase (chromosomal)

(2) intrinsic resistance in gram negatives (decreased uptake)

Bacitracin (topical) ---> Inhibits RNA transcription

Resistance ---> inability to penetrate outer membrane

Antimetabolite Activity

Sulfonamides & Dapsone ---> Compete with *p*-aminobenzoic acid (PABA) preventing synthesis of folic acid

Resistance ---> permeability barriers *(e.g., Pseudomonas)*

Trimethoprim ---> Inhibit dihydrofolate reductase preventing synthesis of folic acid

Resistance --->

(1) decreased affinity of dihydrofolate reductase

(2) intrinsic resistance if use exogenous thymidine

Trimethoprim-Sulfamethoxazole synergism

Characteristics of an Ideal Chemotherapeutic Drug

(There are No Perfect Drugs)

- Selective Toxicity Against Target Pathogen But Not Against Host
  - Would like LD_{50} to be high and Minimal Inhibitory Concentration (MIC) and/or Minimal Bactericidal Concentration (MBC) to be low
    - LD_{50} = Lethal Dose 50%; Measure of drug toxicity/lethality against host
    - MIC; Measure of the concentration of the antibiotic necessary to inhibit growth of the target pathogen
    - MBC; Measure of the concentration of the antibiotic necessary to kill the target pathogen
- Favorable Pharmacokinetics: Survive in high concentration and reach the target site (site of infection)
  - Pharmacokinetics: Action of drugs in the body over a period of time including:
    - Absorption
    - Distribution
    - Localization in tissues

- Biotransformation (biochem. alterations)
- Excretion

- Would Like the Drug to be:

  - **Bactericidal** (Microbicidal): Kills microbes (-cidal = death or killing)

    vs.

  - **Bacteriostatic:** Stops growth of microorganisms without killing them (-static = stationary; at rest; stasis)

- Spectrum of Activity (Broad vs. Narrow) Coordinated with Diagnosis

  - For example:

    - a broad-spectrum antibiotic would be indicated against a polymicrobial infection, e.g., an intrabdominal anaerobic infection

    - a narrow spectrum antibiotic would be ideal for an infection caused by a single pathogen, e.g., a staphylococcal skin infection.

- Lack of "Side Effects"

- Able to Cross Outer and Cytoplasmic Membranes

- No or Low Level of Antibiotic Resistance in Target Pathogen and Lack of Cross-Resistance in Closely Related Strains

- Resistant to Inactivation by Microbial Enzymes

Structures of Beta-Lactam Antibiotics:

Beta-lactam Ring Structure

- Structure of Penicillins
- Structure of Cephalosporins

- Bactericidal Against Actively Growing Cells

- Drug Covalently Links to Cytoplasmic Membrane Regulatory Enzymes (a.k.a., Penicillin binding proteins (PBP))
  - PBPs function in cell to catalyze crosslinking of peptidoglycan chains
  - PBPs are transpeptidases
- Beta-Lactam Antibiotics at Concentrations >MIC:
  - Bind to PBPs
  - Disrupt synthesis of peptidoglycan
  - Resultant release of autolysins (autolytic enzymes)
  - Autolysins enzymatically degrade cell wall forming spheroplast (osmotically-sensitive cell lacking rigidity of cell wall)
  - Cells lyse; Bacterial cell killed
- For *E. coli*, at Concentrations <MIC:
  - Septum formation is interrupted
  - Filamentous, multinucleated cells are observed with cells continuing to divide but septa (new cell walls that separate daughter cells) do not form

Antibiotic Resistance

- Bacterial Resistance to Antibiotics is either:
  1. Intrinsic (inherent) or phenotypic
  2. Acquired via acquisition of foreign resistance genes
  3. Acquired via mutational events in the native genome
- **Intrinsic Resistance:** organism is inherently not susceptible to the antibiotic

Phenotypic Resistance (non-genetic) (e.g., non-growing cells; gram-negative, outer cell membrane)

Genotypic Resistance: Exchange of r-Determinants (Genes that confer resistance to specific antimicrobial agents); Transfer and recombination of resistant mutant genes is possible through normal bacterial genetic exchange mechanisms (conjugation; transduction; transformation)

Plasmids: Multidrug (multiple) resistance is possible; Can cross species barrier and closely related strains may acquire r-determinants

- Plasmid: covalently closed circular extrachromosomal DNA
  - Dispensable
  - May carry genes for drug resistance; metabolic enzymes; virulence factors (e.g., exotoxins)
  - Restricted or broad host range
  - Small size (~5 Md) are non-conjugal; Large (20-200 Md) can be conjugal
- Plasmid transfer between cells
  - Bacterial conjugation ("sex"):Replication and transfer of the conjugal plasmid via cell-to-cell contact through an F-pilus encoded by tra (transfer) genes
  - Transduction: Transferred by phage
  - Transformation possible

Transposons (Tn) (plasmid or chromosomal): Genes transferable within a replicon via self-excision; Multidrug resistance is possible; Can cross species barrier

Integrons found on transposons or plasmids; Contains the gene and the site for incorporating resistance genes as cassettes allowing expression of the genes; Multidrug resistance is possible

Selective chromosomal mutations (single drug resistance)

Physiological and Biochemical Mechanisms of Drug Resistance

Bacteria may Demonstrate any of Five General Mechanisms of Antibiotic Resistance:

1. Lack of entry; Decreased cell permeability
2. Greater exit; Active efflux
3. Enzymatic inactivation of the antibiotic
4. Altered target; Modification of drug receptor site
5. Synthesis of resistant metabolic pathway

These Mechanisms can be Grouped into Three Broad Categories:

- Permeability Mechanisms
- Lack of entry; Decreased cell permeability
- Greater exit; Active efflux
- Enzymatic Inactivation of the Antibiotic
- Altered Target or Pathway
- Altered target; Modification of drug receptor site
- Synthesis of resistant metabolic pathway

Antibiotics by class				
Generic name	**Brand names**	**Common uses**	**Possible side effects**	**Mechanism of action**
Aminoglycosides				
Amikacin	Amikin	Infections caused by Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella*particularly *Pseudomonas aeruginosa*.	• Hearing loss • Vertigo • Kidney damage	Binding to the bacterial 30S ribosomal subunit (some work by binding to the 50S subunit), inhibiting the
Gentamicin	Garamycin			
Kanamycin	Kantrex			
Neomycin	Neo-Fradin[3]			
Netilmicin	Netromycin			

Tobramycin	Nebcin	Effective against Aerobic bacteria (not obligate/facultative anaerobes) and tularemia. All aminoglicocydes are ineffective to be taken orally. Intravenous, intramuscular and topical should be applied.		translocation of the peptidyl-tRNA from the A-site to the P-site and also causing misreading of mRNA, leaving the bacterium unable to synthesize proteins vital to its growth.
Paromomycin	Humatin			
Streptomycin		Tuberculosis		
Spectinomycin(Bs)	Trobicin	Gonorrhea		
Ansamycins				
Geldanamycin		Experimental, as antitumor antibiotics		
Herbimycin				
Rifaximin	Xifaxan	Traveler's diarrhea caused by *E. coli*		
Carbacephem				
Loracarbef	Lorabid	Discontinued		prevents bacterial cell division by inhibiting cell wall synthesis.
Carbapenems				
Ertapenem	Invanz	Bactericidal for both Gram-positive and Gram-negative organisms and therefore useful for empiric broad-spectrum antibacterial coverage. (Note MRSA resistance to	• Gastrointestinal upset and diarrhea • Nausea • Seizures • Headache	Inhibition of cell wall synthesis
Doripenem	Doribax			
Imipenem/Cilastatin	Primaxin			
Meropenem	Merrem			

		this class.)	• Rash and allergic reactions	
Cephalosporins (First generation)				
Cefadroxil	Duricef	Good coverage against Gram-positive infections.	• Gastrointestinal upset and diarrhea • Nausea (if alcohol taken concurrently) • Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cefazolin	Ancef			
Cefalotin or Cefalothin	Keflin(discontinued)			
Cefalexin	Keflex			
Cephalosporins (Second generation)				
Cefaclor	Distaclor	Less Gram-positive cover, improved Gram-negative cover.	• Gastrointestinal upset and diarrhea • Nausea (if alcohol taken concurrently) • Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cefamandole	Mandol(discontinued)			
Cefoxitin	Mefoxin(discontinued)			
Cefprozil	Cefzil			
Cefuroxime	Ceftin, Zinnat(UK)			
Cephalosporins (Third generation)				
Cefixime (antagonistic with	Suprax	Improved coverage of Gram-negative	• Gastrointestinal	Same mode of action as

Chloramphenicol)[4]		organisms, except *Pseudomonas*. Reduced Gram-positive cover. But still not cover*Mycoplasma* and *Chlamydia*	upset and diarrhea • Nausea (if alcohol taken concurrently) • Allergic reactions	other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cefdinir	Omnicef, Cefdiel			
Cefditoren	Spectracef, Meiact			
Cefoperazone [Unlike most third-generation agents, cefoperazone is active against*Pseudomonas aeruginosa*], combination Cefoperazone withSulbactam makes more effective antibiotic, because Sulbactam avoid degeneration of Cefoperazone	Cefobid(discontinued)			
Cefotaxime	Claforan			
Cefpodoxime	Vantin			
Ceftazidime [Unlike most third-generation agents, ceftazidime is active against *Pseudomonas aeruginosa*, but less active against staphylococci	Fortaz			

and streptococci compare to other 3rd generation of Cephalosporins] [5]				
Ceftibuten	Cedax			
Ceftizoxime	Cefizox (discontinued)			
Ceftriaxone [IV and IM, not orally, effective also for syphilisand uncomplicated gonorrhea]	Rocephin			
Cephalosporins (Fourth generation)				
Cefepime	Maxipime	Covers pseudomonal infections.	• Gastrointestinal upset and diarrhea • Nausea (if alcohol taken concurrently) • Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Cephalosporins (Fifth generation)				
Ceftaroline fosamil	Teflaro	Used to treat MRSA	• Gastrointestinal upset and diarrhea • Allergic	Same mode of action as other beta-lactam antibiotics: disrupt the

			reaction	synthesis of thepeptidoglycan layer of bacterial cell walls.
Ceftobiprole	Zeftera	Used to treat MRSA (methicillin-resistant*Staphylococcus aureus*), penicillin-resistant*Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and enterococci	• Gastrointestinal upset and diarrhea • Nausea (if alcohol taken concurrently) • Allergic reactions	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell walls.
Glycopeptides				
Teicoplanin	Targocid (UK)	Active against aerobic and anaerobic Gram-positive bacteria including MRSA; Vancomycin is used orally for the treatment of *C. difficile*		inhibiting peptidoglycan synthesis
Vancomycin	Vancocin			
Telavancin	Vibativ			
Dalbavancin	Dalvance			
Oritavancin	Orbactiv			
Lincosamides(Bs)				
Clindamycin	Cleocin	Serious staph-, pneumo-, and streptococcal infections in penicillin-allergic patients, also anaerobic infections; clindamycin topically foracne	Possible *C. difficile*-relatedpseudomembranous enterocolitis	Bind to 50S subunit of bacterial ribosomal RNAt hereby inhibiting protein synthesis
Lincomycin	Lincocin			

Lipopeptide				
Daptomycin	Cubicin	Gram-positive organisms, but is inhibited by pulmonary surfactant s o less effective against pneumonias		Bind to the membrane and cause rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis
Macrolides(Bs)				
Azithromycin	Zithromax,Sumamed,Xithrone	Streptococcal infections, syphilis, upper respiratory tract infections, lower respiratory tract infections, mycoplasmal infections, Lyme disease	• Nausea, vomiting, and diarrhea (especially at higher doses) • Prolonged cardiac QT interval (especially erythromycin) • Hearing loss (especially at higher doses) • Jaundice	inhibition of bacterial protein biosynthesis by binding reversibly to the subunit 50S of the bacterial ribosome, thereby inhibiting translocation of peptidyl tRNA.
Clarithromycin	Biaxin			
Dirithromycin	Dynabac(discontinued)			
Erythromycin	Erythocin,Erythroped			
Roxithromycin				
Troleandomycin	Tao (discontinued)			
Telithromycin	Ketek	Pneumonia	Visual Disturbance, Liver Toxicity.[6]	
Spiramycin	Rovamycine	Mouth infections		
Monobactams				
Aztreonam	Azactam	Gram-negative bacteria		Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell

				walls.
Nitrofurans				
Furazolidone	Furoxone	Bacterial or protozoal diarrhea or enteritis		
Nitrofurantoin(Bs)	Macrodantin, Macrobid	Urinary tract infections		
Oxazolidinones(Bs)				
Linezolid	Zyvox	VRSA	• Thrombocytopenia • Peripheral neuropathy • Serotonin Syndrome	Protein synthesis inhibitor; prevents the initiation step
Posizolid	Phase II clinical trials			
Radezolid	Phase II clinical trials			
Torezolid	Phase II clinical trials			
Penicillins				
Amoxicillin	Novamox,Amoxil	Wide range of infections; penicillin used forstreptococcal infections, syphilis, and Lyme disease	• Gastrointestinal upset and diarrhea • Allergy with seriousanaphylactic	Same mode of action as other beta-lactam antibiotics: disrupt the synthesis of thepeptidoglycan layer of bacterial cell
Ampicillin	Principen (discontinued)			
Azlocillin				
Carbenicillin	Geocillin (discontinued)			
Cloxacillin	Tegopen (discontinued)			

Dicloxacillin	Dynapen (discontinued)		reactions • Brain and kidney damage (rare)	walls.
Flucloxacillin	Floxapen(Sold to European generics Actavis Group)			
Mezlocillin	Mezlin (discontinued)			
Methicillin	Staphcillin (discontinued)			
Nafcillin	Unipen (discontinued)			
Oxacillin	Prostaphlin (discontinued)			
Penicillin G	Pentids (discontinued)			
Penicillin V	Veetids (Pen-Vee-K) (discontinued)			
Piperacillin	Pipracil (discontinued)			
Penicillin G	Pfizerpen			
Temocillin	Negaban (UK) (discontinued)			
Ticarcillin	Ticar (discontinued)			
Penicillin combinations				
Amoxicillin/clavulanate	Augmentin	Both Amoxicillin/clavulanate and Ampicillin/sulbactam are effective against non-recurrent acute otitis media[7] Only a		The second component prevents bacterialresistance to the first component

		few **oral**-antibiotics active for skin and soft tissue infections, one of it is Amoxicillin/clavulanate. Not to be given to children with less than 40 kilograms weight, for children are heavier, the dosage is same with adult, twice daily [8]		
Ampicillin/sulbactam	Unasyn			
Piperacillin/tazobactam	Zosyn			
Ticarcillin/clavulanate	Timentin			
Polypeptides				
Bacitracin		Eye, ear or bladder infections; usually applied directly to the eye or inhaled into the lungs; rarely given by injection, although the use of intravenous colistin is experiencing a resurgence due to the emergence of multi drug resistant organisms.	Kidney and nerve damage (when given by injection)	Inhibits isoprenyl pyrophosphate, a molecule that carries the building blocks of thepeptidoglycan bacterial cell wall outside of the inner membrane[9]
Colistin	Coly-Mycin-S			Interact with the Gram-negative bacterial outer membrane and cytoplasmic membrane, displacing bacterial
Polymyxin B				

				counterions, which destabilizes the outer membrane. Act like a detergent against the cytoplasmic membrane, which alters its permeability. Polymyxin B and E are bactericidal even in an isosmotic solution.
Quinolones/Fluoroquinolone				
Ciprofloxacin	Cipro,Ciproxin , Ciprobay	Urinary tract infections, bacterial prostatitis, community-acquired pneumonia, bacterial diarrhea, mycoplasmal infections, gonorrhea	Nausea (rare), irreversible damage to central nervous system (uncommon), tendinosis (rare)	inhibit the bacterial DNA gyrase or thetopoisomerase IV enzyme, thereby inhibitingDNA replication and transcription.
Enoxacin	Penetrex			
Gatifloxacin	Tequin			
Gemifloxacin	Factive[10]			
Levofloxacin	Levaquin			
Lomefloxacin	Maxaquin			
Moxifloxacin	Avelox			
Nalidixic acid	NegGram			
Norfloxacin	Noroxin			
Ofloxacin	Floxin (discontinued), Ocuflox			
Trovafloxacin	Trovan	Withdrawn		
Grepafloxacin	Raxar	Withdrawn		
Sparfloxacin	Zagam	Withdrawn		
Temafloxacin	Omniflox	Withdrawn		
Sulfonamides(Bs)				
Mafenide	Sulfamylon	Urinary tract	• Nausea,	Folate

Sulfacetamide	Sulamyd, Bleph-10	infections (except sulfacetamide, used for eye infections, and mafenide and silver sulfadiazine, used topically for burns)	vomiting, and diarrhea • Allergy (including skin rashes) • Crystals in urine • Kidney failure • Decrease in white blood cell count • Sensitivity to sunlight	synthesis inhibition. They arecompetitive inhibitors of the enzymedihydropteroate synthetase, DHPS. DHPS catalyses the conversion of PABA (*para*-aminobenzoate) to dihydropteroate, a key step in folate synthesis. Folate is necessary for the cell to synthesize nucleic acids (nucleic acids are essential building blocks of DNA and RNA), and in its absence cells cannot divide.
Sulfadiazine	Micro-Sulfon			
Silver sulfadiazine	Silvadene			
Sulfadimethoxine	Di-Methox, Albon			
Sulfamethizole	Thiosulfil Forte			
Sulfamethoxazole	Gantanol			
Sulfanilimide (archaic)				
Sulfasalazine	Azulfidine			
Sulfisoxazole	Gantrisin			
Trimethoprim-Sulfamethoxazole(Co-trimoxazole) (TMP-SMX)	Bactrim, Septra			
Sulfonamidochrysoidine(archaic)	Prontosil			
Tetracyclines(Bs)				
Demeclocycline	Declomycin	Syphilis, chlamydial infections, Lyme disease,mycoplasmal infections, acne rickettsialinfections, *malaria *Note: Malaria is caused by a protist and not a bacterium.	• Gastrointestinal upset • Sensitivity to sunlight • Potential	inhibiting the binding of aminoacyl-tRNA to themRNA-ribosome complex. They do so mainly by binding to
Doxycycline	Vibramycin			
Minocycline	Minocin			
Oxytetracycline	Terramycin			
Tetracycline	Sumycin,Achromycin V,Steclin			

			toxicity to mother and fetus during pregnancy • Enamel hypoplasia (staining of teeth; potentially permanent) • transient depression of bone growth	the 30S ribosomal subunit in themRNA translation complex. But Tetracycline cannot be taken together with all dairy products, aluminium, iron and zinc minerals.
Drugs against mycobacteria				
Clofazimine	Lamprene	Antileprotic		
Dapsone	Avlosulfon	Antileprotic		
Capreomycin	Capastat	Antituberculosis		
Cycloserine	Seromycin	Antituberculosis, urinary tract infections		
Ethambutol(Bs)	Myambutol	Antituberculosis		
Ethionamide	Trecator	Antituberculosis		Inhibits peptide synthesis
Isoniazid	I.N.H.	Antituberculosis		
Pyrazinamide	Aldinamide	Antituberculosis		
Rifampicin (Rifampin in US)	Rifadin, Rimactane	mostly Gram-positive and mycobacteria	Reddish-orange sweat, tears, and urine	Binds to the β subunit of RNA polymerase to inhibit

				transcription
Rifabutin	Mycobutin	*Mycobacterium avium* complex	Rash, discolored urine, GI symptoms	
Rifapentine	Priftin	Antituberculosis		
Streptomycin		Antituberculosis	Neurotoxicity, ototoxicity	As other aminoglycosides
Others				
Arsphenamine	Salvarsan	Spirochaetal infections (obsolete)		
Chloramphenicol(Bs)	Chloromycetin	Meningitis, MRSA, topical use, or for low-cost internal treatment. Historic: typhus, cholera.Gram-negative, Gram-positive, anaerobes	Rarely: aplastic anemia.	Inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome
Fosfomycin	Monurol, Monuril	Acute cystitis in women	This antibiotic is not recommended for children and 75 up of age	Inactivates enolpyruvyl transferase, thereby blocking cell wall synthesis
Fusidic acid	Fucidin			
Metronidazole	Flagyl	Infections caused by anaerobic bacteria; alsoamoebiasis, trichomoniasis, giardiasis	Discolored urine,headache, metallic taste,nausea; alcohol is contraindicated	Produces toxic free radicals that disrupt DNA and proteins. This non-specific mechanism is responsible for its activity

				against a variety of bacteria, amoebae, and protozoa.
Mupirocin	Bactroban	Ointment for impetigo, cream for infected cuts		Inhibits isoleucine t-RNA synthetase (IleRS) causing inhibition of protein synthesis
Platensimycin				
Quinupristin/Dalfopristin	Synercid			
Thiamphenicol		Gram-negative, Gram-positive, anaerobes. Widely used in veterinary medicine.	Rash. Lacks known anemic side-effects.	A chloramphenicol analog. May inhibit bacterial protein synthesis by binding to the 50S subunit of the ribosome
Tigecycline(Bs)	Tigacyl	Slowly Intravenous. Indicated for complicated skin/skin structure infections, soft tissues infections and complicated intra-abdominal infections. Effective for gram positive and negative and also anaerob antibiotics, against multi-resistant antibiotics bacteries such as*Staphylococcus aureus* (MRSA) and*Acinetobacter baumannii*, but not	Teeth discoloration and same side effects astetracycline. Not to be given for children and pregnant or lactate women. Relatively safe and no need dose adjusted when be given for mild to	Similar structure with tetracycline, but 5 times stronger, big volume distribution and long half-time in the body

		effective for*Pseudomonas* spp. and *Proteus* spp.	moderate liver function or renal patients	
Tinidazole	Tindamax Fasigyn	Protozoal infections	Upset stomach, bitter taste, and itchiness	
Trimethoprim(Bs)	Proloprim, Trimpex	Urinary tract infections		
Generic Name	**Brand Names**	**Common Uses**[2]	**Possible Side Effects**[2]	**Mechanism of action**