REVIEW ARTICLE

Review: A Perspective Use and Misuse of Antibiotics

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Abstract

Antibiotics are the most active chemotherapeutics among drugs; they exert their therapeutic effect by antagonizing the growth of bacteria. Since 1910 many antibiotics have been developed with different mechanisms of action including: (1) Inhibition of bacteria's cell wallsynthesis; this class of antibiotics includes vancomycin and β-lactam antibiotics such aspenicillins, cephalosporins, and carbapenems, (2) inhibition of protein synthesis including tetracyclines, aminoglycosides, macrolides, and chloramphenicol, and (3) DNA synthesis inhibitors such as fluoroquinolones and sulfonamides that inhibit folic acid synthesis. In this chapter, we describe the three antibiotic classes, their mechanism of action, clinical uses, side effects, and their resistance by different bacteria.

Key words: Antibiotics, bacterial resistance, bacteria's cell wall synthesis inhibitors

INTRODUCTION

An antibiotic is a type of antimicrobial substance active against bacteria. It is the most important type of antibacterial agent for fighting bacterial infections, and antibiotic medications are widely used in the treatment and prevention of such infections.[1] They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess antiprotozoal activity.[2] Antibiotics are not effective against viruses such as the common cold or influenza, drugs which inhibit growth of viruses are termed antiviral drugs or antivirals rather than antibiotics. They are also not effective against fungi; drugs which inhibit growth of fungi are called antifungal drugs.

Sometimes, the term *antibiotic* – literally "opposing life," from the Greek roots ἀντι*anti*, "against" and βίος*bios*, "life" – is broadly used to refer to any substance used against microbes, but in the usual medical usage, antibiotics (such as penicillin) are those produced naturally (by one microorganism fighting another whereas non-antibiotic antibacterials (such as sulfonamides and antiseptics) are fully synthetic. However, both classes have the same goal of killing or preventing the growth of micro), organisms, and both are included in antimicrobial chemotherapy. "Antibacterials" include antiseptic drugs, antibacterial soaps, and chemical disinfectants, whereas antibiotics are an important class of antibacterials used more specifically in medicine[3] and sometimes in livestock feed.

Antibiotics have been used since ancient times. Many civilizations used topical application of moldy bread, with many references to its beneficial effects arising from ancient Egypt, Nubia, China, Serbia, Greece, and Rome.[4] The first person to directly document the use of molds to treat infections was John Parkinson (1567–1650). Antibiotics revolutionized medicine in the 20th century. Alexander Fleming (1881–1955) discovered modern day penicillin in 1928, the widespread use of which proved significantly beneficial during wartime. However, the effectiveness and easy access to antibiotics have also led to their overuse[5] and

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some bacteria have evolved resistance to them. The World Health Organization (WHO) has classified antimicrobial resistance as a widespread "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".[6] Global deaths attributable to antimicrobial resistance numbered 1.27 million in 2019.

HISTORY OF ANTIBIOTIC

Antibiotics have been around since 1928 when penicillin was discovered by Alexander Fleming. In the 1980s, antibiotics that were determined medically important for treatment of animals could be approved under veterinary oversight. In 1996, the National Antimicrobial Resistance Monitoring System (NARMS) was established. Starting in 2010, publications regarding antimicrobial drugs in food became an annual report. Starting in 2012, there was publicly solicited input on how data are to be collected and reported for matters relating to the use of antimicrobials for food-producing animals. Resulting from this, the Food and Drug Administration (FDA) revised its sampling structure within NARMS with the goal of obtaining more representative livestock data for the key organisms under surveillance. "NARMS partners at Centers of Disease Control and Prevention (CDC) and United States Department of Agriculture (USDA) have published over 150 peer-reviewed research articles examining the nature and magnitude of antimicrobial resistance hazards associated with antibiotic use in food-producing animals." In 2014, the FDA began working with the USDA and the CDC to explore additional mechanisms to obtain data that are representative of antibiotic use in food-producing animals. In 2015, the FDA issued the Veterinary Feed Directive final rule, under which veterinarians must authorize the use of antimicrobials within feed for the animals they serve.

In addition to antibiotic regulation in food production, there have been numerous policies put in place to regulate antibiotic distribution in healthcare, specifically in hospital settings. In 2014, the CDC officially recognized the need for antimicrobial stewardship within all U.S. hospitals in their publication of the Core Elements of Hospital Antibiotic Stewardship Programs. These programs outline opportunities for reducing unnecessary antibiotic usage, and provide guidelines for antibiotic prescription for common infections. The CDC highlighted post-prescription tactics for antibiotic regulation, such as reassessing dosages and the class or type of antibiotic used, to optimally treat each infection. The CDC also emphasized the need for evidence-based prescribing, a practice that focuses on the utilization of evidence and research to make informed medical decisions; these sentiments were echoed by the American Dental Association which works to provide detailed guidelines for dentists considering prescribing their patients antibiotics.[7] In 2019, the CDC published a report concerning the issue and updating the public on the effectiveness of past policy. This report, titled antibiotic resistance threats in the United States, 2019, indicated which pathogens posed the greatest threat of resistance, and highlighted the importance of infection prevention, providing recommendations for prevention strategies.[8]

There has also been a substantial effort to educate not only prescribers, but patients too on the issue of antibiotic misuse. The WHO has designated a "World Antimicrobial Awareness Week" in November. In 2021, the week's theme was "spread awareness, stop resistance" and the organization published many different forms of media including podcasts, articles, and infographics to raise awareness for the issue.[7] In the United States, the CDC has published posters and other materials for the purpose of educating the public on antibiotic resistance. State health departments, such as Colorado's Department of Public Health and Environment, have partnered with the CDC to distribute these materials to healthcare providers.

PRODUCTION

With advances in medicinal chemistry, most modern antibacterials are semisynthetic modifications of various natural compounds. 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. Many antibacterial compounds are relatively small molecules with a molecular weight of <1000 daltons.[9]

Since the first pioneering efforts of Howard 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.

PENICILLIN AND OTHER NATURAL ANTIBIOTICS

Observations about the growth of some microorganisms inhibiting the growth of other microorganisms have been reported since the late 19th century. These observations of antibiosis between microorganisms led to the discovery of natural antibacterials. Louis Pasteur observed, "if we could intervene in the antagonism observed between some bacteria, it would offer perhaps the greatest hopes for therapeutics."

In 1874, physician Sir William Roberts noted that cultures of the mold *Penicillium glaucum* that is used in the making

of some types of blue cheese did not display bacterial contamination. In 1876, physicist John Tyndall also contributed to this field.

In 1895 Vincenzo Tiberio, Italian physician, published a paper on the antibacterial power of some extracts of mold.[10]

In 1897, doctoral student Ernest Duchesne submitted a dissertation, "Contribution à l'étude de la concurrence vitale chez les micro-organismes: Antagonisme entre les moisissures et les microbes" (Contribution to the study of vital competition in micro-organisms: Antagonism between molds and microbes),[11] the first known scholarly work to consider the therapeutic capabilities of molds resulting from their anti-microbial activity. In his thesis, Duchesne proposed that bacteria and molds engage in a perpetual battle for survival. Duchesne observed that *Escherichia coli* was eliminated by *P. glaucum* when they were both grown in the same culture. He also observed that when he inoculated laboratory animals with lethal doses of typhoid bacilli together with *P. glaucum*, the animals did not contract typhoid. Duchesne's army service after getting his degree prevented him from doing any further research.[12] Duchesne died of tuberculosis, a disease now treated by antibiotics.

In 1928, Sir Alexander Fleming postulated the existence of penicillin, a molecule produced by certain molds that kills or stops the growth of certain kinds of bacteria. Fleming was working on a culture of disease-causing bacteria when he noticed the spores of a green mold, *Penicillium rubens*,[13] in one of his culture plates. He observed that the presence of the mold killed or prevented the growth of the bacteria. Fleming postulated that the mold must secrete an antibacterial substance, which he named penicillin in 1928. Fleming believed that its antibacterial properties could be exploited for chemotherapy. He initially characterized some of its biological properties, and attempted to use a crude preparation to treat some infections, but he was unable to pursue its further development without the aid of trained chemists.[14]

Ernst Chain, Howard Florey, and Edward Abraham succeeded in purifying the first penicillin, penicillin G, in 1942, but it did not become widely available outside the allied military before 1945. Later, Norman Heatley developed the back extraction technique for efficiently purifying penicillin in bulk. The chemical structure of penicillin was first proposed by Abraham in 1942 and then later confirmed by Dorothy Crowfoot Hodgkin in 1945. Purified penicillin displayed potent antibacterial activity against a wide range of bacteria and had low toxicity in humans. Furthermore, its activity was not inhibited by biological constituents such as pus, unlike the synthetic sulfonamides. The development of penicillin led to renewed interest in the search for antibiotic compounds with similar efficacy and safety. For their successful development of penicillin, which Fleming had accidentally discovered but could not develop himself, as a therapeutic drug, Chain and Florey shared the 1945 Nobel Prize in Medicine with Fleming.[15]

Florey credited René Dubos with pioneering the approach of deliberately and systematically searching for antibacterial compounds, which had led to the discovery of gramicidin and had revived Florey's research in penicillin. In 1939, coinciding with the start of World War II, Dubos had reported the discovery of the first naturally derived antibiotic, tyrothricin, a compound of 20% gramicidin and 80% tyrocidine, from *Bacillus brevis*. It was one of the first commercially manufactured antibiotics and was very effective in treating wounds and ulcers during World War II.[16] Gramicidin, however, could not be used systemically because of toxicity. Tyrocidine also proved too toxic for systemic usage. Research results obtained during that period were not shared between the Axis and the Allied powers during World War II and limited access during the Cold War.

REPLENISHING THE ANTIBIOTIC PIPELINE AND DEVELOPING OTHER NEW THERAPIES

Because antibiotic-resistant bacterial strains continue to emerge and spread, there is a constant need to develop new antibacterial treatments. Current strategies include traditional chemistry-based approaches such as natural product-based drug discovery, newer chemistry-based approaches such as drug design, traditional biology-based approaches such as immunoglobulin therapy, and experimental biology-based approaches such as phage therapy, fecal microbiota transplants, antisense RNA-based treatments, and CRISPR-Cas9-based treatments.[17]

NATURAL PRODUCT-BASED ANTIBIOTIC DISCOVERY

Most of the antibiotics in current use are natural products or natural product derivatives, and bacterial, fungal, plant, and animal extracts are being screened in the search for new antibiotics. Organisms may be selected for testing based on ecological, ethnomedical, genomic, or historical rationales. Medicinal plants, for example, are screened on the basis that they are used by traditional healers to prevent or cure infection and may therefore contain antibacterial compounds. Furthermore, soil bacteria are screened on the basis that, historically, they have been a very rich source of antibiotics (with 70–80% of antibiotics in current use derived from the actinomycetes).[18]

In addition to screening natural products for direct antibacterial activity, they are sometimes screened for the ability to suppress antibiotic resistance and antibiotic tolerance. For example, some secondary metabolites inhibit

drug efflux pumps, thereby increasing the concentration of antibiotic able to reach its cellular target and decreasing bacterial resistance to the antibiotic. Natural products known to inhibit bacterial efflux pumps include the alkaloidlysergol, the carotenoids capsanthin and capsorubin, and the flavonoids rotenone and chrysin. Other natural products, this time primary metabolites rather than secondary metabolites, have been shown to eradicate antibiotic tolerance. For example, glucose, mannitol, and fructose reduce antibiotic tolerance in *E. coli* and *Staphylococcus aureus*, rendering them more susceptible to killing by aminoglycoside antibiotics.

Natural products may be screened for the ability to suppress bacterial virulence factors too. Virulence factors are molecules, cellular structures and regulatory systems that enable bacteria to evade the body's immune defenses (e.g., urease and staphyloxanthin), move towards, attach to, and/or invade human cells (e.g., type IV pili, adhesins, and internalins), coordinate the activation of virulence genes (e.g., quorum sensing), and cause disease (e.g., exotoxins). Examples of natural products with antivirulence activity include the flavonoid epigallocatechin gallate (which inhibits listeriolysin O), the quinonetetrangomycin (which inhibits staphyloxanthin), and the sesquiterpene zerumbone (which inhibits *Acinetobacter baumannii* motility).

IMMUNOGLOBULIN THERAPY

Monoclonal antibody therapy

Antibodies (anti-tetanus immunoglobulin) have been used in the treatment and prevention of tetanus since the 1910s,[19] and this approach continues to be a useful way of controlling bacterial diseases. The monoclonal antibodybezlotoxumab, for example, has been approved by the US FDA and EMA for recurrent *Clostridium difficile* infection, and other monoclonal antibodies are in development (e.g., AR-301 for the adjunctive treatment of *S. aureus* ventilator-associated pneumonia). Antibody treatments act by binding to and neutralizing bacterial exotoxins and other virulence factors.

Phage therapy

Phage therapy is under investigation as a method of treating antibiotic-resistant strains of bacteria. Phage therapy involves infecting bacterial pathogens with viruses. Bacteriophages and their host ranges are extremely specific for certain bacteria, thus, unlike antibiotics, they do not disturb the host organism's intestinal microbiota. Bacteriophages, also known as phages, infect and kill bacteria primarily during lytic cycles. Phages insert their DNA into the bacterium, where it is transcribed and used to make new phages, after which the cell will lyse, releasing new phage that are able to infect and destroy further bacteria of the same strain. The high specificity of phage protects "good" bacteria from destruction.

Some disadvantages to the use of bacteriophages also exist, however. Bacteriophages may harbor virulence factors or toxic genes in their genomes and, before use, it may be prudent to identify genes with similarity to known virulence factors or toxins by genomic sequencing. In addition, the oral and IV administration of phages for the eradication of bacterial infections poses a much higher safety risk than topical application. Furthermore, there is the additional concern of uncertain immune responses to these large antigenic cocktails.

There are considerable regulatory hurdles that must be cleared for such therapies.[20] Despite numerous challenges, the use of bacteriophages as a replacement for antimicrobial agents against MDR pathogens that no longer respond to conventional antibiotics, remains an attractive option.

FECAL MICROBIOTA TRANSPLANTS

Fecal microbiota transplants involve transferring the full intestinal microbiota from a healthy human donor (in the form of stool) to patients with *C. difficile* infection. Although this procedure has not been officially approved by the US FDA, its use is permitted under some conditions in patients with antibiotic-resistant *C. difficile* infection. Cure rates are around 90%, and work is underway to develop stool banks, standardized products, and methods of oral delivery.

ANTISENSE RNA-BASED TREATMENTS

Further information: Antisense RNA

Antisense RNA-based treatment (also known as gene silencing therapy) involves (a) identifying bacterial genes that encode essential proteins (e.g., the *Pseudomonas aeruginosa* genes *acpP*, *lpxC*, and *rpsJ*), (b) synthesizing single stranded RNA that is complementary to the mRNA encoding these essential proteins, and (c) delivering the single stranded RNA to the infection site using cell-penetrating peptides or liposomes. The antisense RNA then hybridizes with the bacterial mRNA and blocks its translation into the essential protein. Antisense RNA-based treatment has been shown to be effective in *in vivo* models of *P. aeruginosa* pneumonia.

In addition to silencing essential bacterial genes, antisense RNA can be used to silence bacterial genes responsible for antibiotic resistance. For example, antisense RNA has been developed that silences the *S. aureus mecA* gene (the gene that encodes modified penicillin-binding protein 2a and renders *S. aureus* strains methicillin-resistant). Antisense RNA targeting *mecA* mRNA has been shown to restore the susceptibility of methicillin-resistant staphylococci to oxacillin in both *in vitro* and *in vivo* studies.[21]

CRISPR-CAS9-BASED TREATMENTS

In the early 2000s, a system was discovered that enables bacteria to defend themselves against invading viruses. The system, known as CRISPR-Cas9, consists of (a) an enzyme that destroys DNA (the nucleaseCas9) and (b) the DNA sequences of previously encountered viral invaders (CRISPR). These viral DNA sequences enable the nuclease to target foreign (viral) rather than self (bacterial) DNA.

Although the function of CRISPR-Cas9 in nature is to protect bacteria, the DNA sequences in the CRISPR component of the system can be modified so that the Cas9 nuclease targets bacterial resistance genes or bacterial virulence genes instead of viral genes. The modified CRISPR-Cas9 system can then be administered to bacterial pathogens using plasmids or bacteriophages. This approach has successfully been used to silence antibiotic resistance and reduce the virulence of enterohemorrhagic *E. coli* in an *in vivo* model of infection.

SYNTHETIC ANTIBIOTICS DERIVED FROM DYES

Synthetic antibiotic chemotherapy as a science and development of antibacterials began in Germany with Paul Ehrlich in the late 1880s. Ehrlich noted certain dyes would color human, animal, or bacterial cells, whereas others did not. He then proposed the idea that it might be possible to create chemicals that would act as a selective drug that would bind to and kill bacteria without harming the human host. After screening hundreds of dyes against various organisms, in 1907, he discovered a medicinally useful drug, the first synthetic antibacterial organoarsenic compounds alvarsan,[22] now called arsphenamine.

This heralded the era of antibacterial treatment that was begun with the discovery of a series of arsenic-derived synthetic antibiotics by both Alfred Bertheim and Ehrlich in 1907. Ehrlich and Bertheim had experimented with various chemicals derived from dyes to treat trypanosomiasis in mice and spirochaeta infection in rabbits. While their early compounds were too toxic, Ehrlich and Sahachiro Hata, a Japanese bacteriologist working with Erlich in the quest for a drug to treat syphilis, achieved success with the 606th compound in their series of experiments. In 1910, Ehrlich and Hata announced their discovery, which they called drug "606," at the Congress for Internal Medicine at Wiesbaden. The Hoechst company began to market the compound toward the end of 1910 under the name Salvarsan, now known as arsphenamine. The drug was used to treat syphilis in the first half of the 20th century. In 1908, Ehrlich received the Nobel Prize in Physiology or Medicine for his contributions to immunology. Hata was nominated for the Nobel Prize in Chemistry in 1911 and for the Nobel Prize in Physiology or Medicine in 1912 and 1913.

The first sulfonamide and the first systemically active antibacterial drug, Prontosil, was developed by a research team led by Gerhard Domagk in 1932 or 1933 at the Bayer Laboratories of the IG Farben conglomerate in Germany, for which Domagk received the 1939 Nobel Prize in Physiology or Medicine. Sulfanilamide, the active drug of Prontosil, was not patentable as it had already been in use in the dye industry for some years. Prontosil had a relatively broad effect against Gram-positive cocci, but not against Enterobacteria. Research was stimulated apace by its success. The discovery and development of this sulfonamide drug opened the era of antibacterials.

MEDICAL USES

Antibiotics are used to treat or prevent bacterial infections, and sometimes protozoan infections. (Metronidazole is effective against a number of parasitic diseases). When an infection is suspected of being responsible for an illness but the responsible pathogen has not been identified, an empiric therapy is adopted. This involves the administration of a broad-spectrum antibiotic based on the signs and symptoms presented and is initiated pending laboratory results that can take several days.[23]

When the responsible pathogenic microorganism is already known or has been identified, definitive therapy can be started. This will usually involve the use of a narrow-spectrum antibiotic. The choice of antibiotic given will also be based on its cost. Identification is critically important as it can reduce the cost and toxicity of the antibiotic therapy and also reduce the possibility of the emergence of antimicrobial resistance. To avoid surgery, antibiotics may be given for non-complicated acute appendicitis.

Antibiotics may be given as a preventive measure and this is usually limited to at-risk populations such as those with a weakened immune system (particularly in HIV cases to prevent pneumonia), those taking immunosuppressive drugs, cancer patients, and those having surgery. Their use in surgical procedures is to help prevent infection of incisions. They have an important role in dental antibiotic prophylaxis where their use may prevent bacteremia and consequent infective endocarditis. Antibiotics are also used to prevent infection in cases of neutropenia particularly cancer-related.

The use of antibiotics for secondary prevention of coronary heart disease is not supported by current scientific evidence, and may actually increase cardiovascular mortality, all-cause mortality and the occurrence of stroke.

ROUTES OF ADMINISTRATION

There are many different routes of administration for antibiotic treatment. Antibiotics are usually taken by mouth. In more

severe cases, particularly deep-seated systemic infections, antibiotics can be given intravenously or by injection. Where the site of infection is easily accessed, antibiotics may be given topically in the form of eye drops onto the conjunctiva for conjunctivitis or ear drops for ear infections and acute cases of swimmer's ear. Topical use is also one of the treatment options for some skin conditions including acne and cellulitis. Advantages of topical application include achieving high and sustained concentration of antibiotic at the site of infection; reducing the potential for systemic absorption and toxicity, and total volumes of antibiotic required are reduced, thereby also reducing the risk of antibiotic misuse.[24] Topical antibiotics applied over certain types of surgical wounds have been reported to reduce the risk of surgical site infections. However, there are certain general causes for concern with topical administration of antibiotics. Some systemic absorption of the antibiotic may occur; the quantity of antibiotic applied is difficult to accurately dose, and there is also the possibility of local hypersensitivity reactions or contact dermatitis occurring. It is recommended to administer antibiotics as soon as possible, especially in life-threatening infections. Many emergency departments stock antibiotics for this purpose.

SIDE EFFECTS

Antibiotics are screened for any negative effects before their approval for clinical use and are usually considered safe and well tolerated. However, some antibiotics have been associated with a wide extent of adverse side effects ranging from mild to very severe depending on the type of antibiotic used, the microbes targeted, and the individual patient. Side effects may reflect the pharmacological or toxicological properties of the antibiotic or may involve hypersensitivity or allergic reactions. Adverse effects range from fever and nausea to major allergic reactions, including photodermatitis and anaphylaxis.

Common side effects of oral antibiotics include diarrhea, resulting from disruption of the species composition in the intestinal flora, resulting, for example, in overgrowth of pathogenic bacteria, such as *C. difficile*. Taking probiotics during the course of antibiotic treatment can help prevent antibiotic-associated diarrhea. Antibacterials can also affect the vaginal flora, and may lead to overgrowth of yeast species of the genus *Candida* in the vulvo-vaginal area. Additional side effects can result from interaction with other drugs, such as the possibility of tendon damage from the administration of a quinolone antibiotic with a systemic corticosteroid.[25]

Some antibiotics may also damage the mitochondrion, a bacteria-derived organelle found in eukaryotic, including human, cells. Mitochondrial damage cause oxidative stress in cells and has been suggested as a mechanism for side effects from fluoroquinolones.

INTERACTIONS

Birth control pills

There are few well-controlled studies on whether antibiotic use increases the risk of oral contraceptive failure. The majority of studies indicate antibiotics do not interfere with birth control pills, such as clinical studies that suggest the failure rate of contraceptive pills caused by antibiotics is very low (about 1%). Situations that may increase the risk of oral contraceptive failure include non-compliance (missing taking the pill), vomiting, or diarrhea. Gastrointestinal disorders or interpatient variability in oral contraceptive absorption affecting ethinylestradiolserum levels in the blood. Women with menstrual irregularities may be at higher risk of failure and should be advised to use backup contraception during antibiotic treatment and for 1 week after its completion. If patient-specific risk factors for reduced oral contraceptive efficacy are suspected, backup contraception is recommended.

In cases where antibiotics have been suggested to affect the efficiency of birth control pills, such as for the broad-spectrum antibiotic 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 antibiotics that are suspected to interact with oral contraceptives. More studies on the possible interactions between antibiotics and birth control pills (oral contraceptives) are required as well as careful assessment of patient-specific risk factors for potential oral contractive pill failure before dismissing the need for backup contraception.

Alcohol

Interactions between alcohol and certain antibiotics may occur and may cause side effects and decreased effectiveness of antibiotic therapy. While moderate alcohol consumption is unlikely to interfere with many common antibiotics, there are specific types of antibiotics with which alcohol consumption may cause serious side effects.[26] Therefore, potential risks of side effects and effectiveness depend on the type of antibiotic administered.

Antibiotics such as 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. In addition, the efficacy of doxycycline and erythromycin succinate may be reduced by alcohol consumption.[27] Other effects of alcohol on antibiotic activity include altered activity of the liver enzymes that break down the antibiotic compound.

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. The bactericidal activity of antibacterials may depend on the bacterial growth phase, and it often requires ongoing metabolic activity and division of bacterial cells. These findings are based on laboratory studies, and in clinical settings have also been shown to eliminate bacterial infection. Since the activity of antibacterials depends frequently on its concentration, *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.

COMBINATION THERAPY

In important infectious diseases, including tuberculosis, combination therapy (i.e., the concurrent application of two or more antibiotics) has been used to delay or prevent the emergence of resistance. In acute bacterial infections, antibiotics as part of combination therapy are prescribed for their synergistic effects to improve treatment outcome as the combined effect of both antibiotics is better than their individual effect. Methicillin-resistant *S. aureus* infections may be treated with a combination therapy of fusidic acid and rifampicin. Antibiotics used in combination may also be antagonistic and the combined effects of the two antibiotics may be less than if one of the antibiotics was given as a monotherapy. For example, chloramphenicol and tetracyclines are antagonists to penicillins. However, this can vary depending on the species of bacteria. In general, combinations of a bacteriostatic antibiotic and bactericidal antibiotic are antagonistic.

In addition to combining one antibiotic with another, antibiotics are sometimes co-administered with resistance-modifying agents. For example, β-lactam antibiotics may be used in combination with β-lactamase inhibitors, such as clavulanic acid or sulbactam, when a patient is infected with a β-lactamase-producing strain of bacteria.

Antibiotic misuse, sometimes called antibiotic abuse or antibiotic overuse, refers to the misuse or overuse of antibiotics, with potentially serious effects on health. It is a contributing factor to the development of antibiotic resistance, including the creation of multidrug-resistant bacteria, informally called "super bugs:" Relatively harmless bacteria (such as *Staphylococcus*, *Enterococcus,* and *Acinetobacter*) can develop resistance to multiple antibiotics and cause life-threatening infections.

"The first rule of antibiotics is to try not to use them, and the second rule is try not to use too many of them." Inappropriate antibiotic treatment and overuse of antibiotics have contributed to the emergence of antibiotic-resistant bacteria. However, potential harm from antibiotics extends beyond selection of antimicrobial resistance and their overuse is associated with adverse effects for patients themselves, seen most clearly in critically ill patients in intensive care units. Self-prescribing 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. Furthermore, incorrect or suboptimal antibiotics are prescribed for certain bacterial infections.[23] The overuse of antibiotics, such as 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.[28]

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 on respiratory tract infections found "physicians were more likely to prescribe antibiotics to patients who appeared to expect them." Multifactorial interventions aimed at both physicians and patients can reduce inappropriate prescription of antibiotics. The lack of rapid point of care diagnostic tests, particularly in resource-limited settings is considered one of the drivers of antibiotic misuse.

INSTANCES OF ANTIBIOTIC MISUSE

Antibiotics treats bacterial infections rather than viral infections

Common situations in which antibiotics are overused include the following:[3]

- Apparent viral respiratory illness in children should not be treated with antibiotics. If there is a diagnosis of bacterial infection, then antibiotics may be used
- Despite acute respiratory-tract infections being mainly caused by viruses, as many as 75% of cases are treated with antibiotics
- When children with ear tubes get ear infections, they should have antibiotic eardrops put into their ears to go to the infection rather than having oral antibiotics, which are more likely to have unwanted side effects
- Swimmer's ear should be treated with antibiotic eardrops, not oral antibiotics
- Sinusitis should not be treated with antibiotics because it is usually caused by a virus, and even when it is caused by a

bacterium, antibiotics are not indicated except in atypical circumstances as it usually resolves without treatment
- Viral conjunctivitis should not be treated with antibiotics. Antibiotics should only be used with confirmation that a patient has bacterial conjunctivitis
- Older persons often have bacteria in their urine which is detected in routine urine tests, but unless the person has the symptoms of a urinary tract infection, antibiotics should not be used in response
- Eczema should not be treated with oral antibiotics. Dry skin can be treated with lotions or other symptom treatments
- The use of topical antibiotics to treat surgical wounds does not reduce infection rates in comparison with non-antibiotic ointment or no ointment at all
- The use of doxycycline in acne vulgaris has been associated with increased risk of Crohn's disease
- The use of minocycline in acne vulgaris has been associated with skin and gut dysbiosis.

Antibiotic resistance

Although antibiotics are required to treat severe bacterial infections, misuse has contributed to a rise in bacterial resistance. The overuse of fluoroquinolone and other antibiotics fuels antibiotic resistance in bacteria, which can inhibit the treatment of antibiotic-resistant infections. Their excessive use in children with otitis media has given rise to a breed of bacteria resistant to antibiotics entirely.[29] In addition, the use of antimicrobial substances in building materials and personal care products has contributed to a higher percentage of antibiotic resistant bacteria in the indoor environment, where humans spend a large majority of their lives.

Widespread use of fluoroquinolones as a first-line antibiotic has led to decreased antibiotic sensitivity, with negative implications for serious bacterial infections such as those associated with cystic fibrosis, where quinolones are among the few viable antibiotics.

Inappropriate use

Antibiotics are important drugs. Many antibiotics can successfully treat infections caused by bacteria (bacterial infections). Antibiotics can prevent the spread of disease. And antibiotics can reduce serious disease complications.

But some antibiotics that used to be typical treatments for bacterial infections now don't work as well. And some drugs do not work at all against some bacteria. When an antibiotic no longer works against some strains of bacteria, those bacteria are said to be antibiotic resistant. Antibiotic resistance is one of the world's most urgent health problems.

The overuse and misuse of antibiotics are key factors leading to antibiotic resistance. The general public, health-care providers and hospitals all can help ensure correct use of the drugs. This can lessen the growth of antibiotic resistance.

Bacteria resist a drug when the bacteria change in some way. The change may protect the bacteria from the drug's effects or limit the drug's access to the bacteria. Or the change may cause the bacteria to change the drug or destroy it.

Bacteria that survive an antibiotic treatment can multiply and pass on resistant properties. Furthermore, some bacteria can pass on their drug-resistant properties to other bacteria. This is similar to them passing along tips to help each other survive.

The fact that bacteria develop resistance to a drug is normal and expected. But the way that drugs are used affects how quickly and to what degree resistance occurs.

Overuse of antibiotics

The overuse of antibiotics – especially taking antibiotics when they are not the correct treatment – promotes antibiotic resistance. According to the centers for disease control and prevention, about one-third of antibiotic use in people is neither needed nor appropriate.

Antibiotics treat infections caused by bacteria. But they do not treat infections caused by viruses (viral infections). For example, an antibiotic is the correct treatment for strep throat, which is caused by bacteria. But it's not the right treatment for most sore throats, which are caused by viruses.

Other common viral infections that are not helped by the use of antibiotics include

- Cold or runny nose
- Flu (influenza)
- Bronchitis
- Most coughs
- Some ear infections
- Some sinus infections
- Stomach flu
- Corona virus disease 2019 (COVID-19)

Taking an antibiotic for a viral infection

- Won't cure the infection
- Won't keep other people from getting sick
- Won't help you or your child feel better
- May cause needless and harmful side effects
- Promotes antibiotic resistance.

If you take an antibiotic when you have a viral infection, the antibiotic attacks bacteria in your body. These are bacteria that are helpful or are not causing disease. This incorrect treatment can then promote antibiotic-resistant properties in harmless bacteria that can be shared with other bacteria. Or it can create an opportunity for potentially harmful bacteria to replace the harmless ones.

Common examples of avoidable antibiotic misuse in clinics

(1) Unadequate dosing; (2) unnecessary wide spectrum; (3) unnecessary double anaerobic coverage; (4) limited intravenous-to-oral shift; (5) unnecessary long antibiotic therapy duration; (6) limited access to outpatient parenteral antibiotic therapy; (7) limited exploitation of the PK/PD potential of a certain antibiotic; (8) limited clinical use of biomarkers; (9) limited knowledge of old (but effective) antibiotics; and (10) limited antibiotic allergy de-labeling.

CONCLUSION

The usage of antibiotics without a medical prescription leads to misuse of antibiotics and encouraging the public to practice the habit. Medical practitioners practice of writing antibiotics especially the newer generation of antibiotics without a culture sensitivity test will be a strong reason in future for antibiotic resistance. Antibiotics are double sided weapon if not used properly it may be dangerous to the user. Antibiotic therapy in the community must be improved through better patient and physician education of appropriate antibiotic use, and use of antibiotics with simpler dosing regimens that can minimize the misuse of antibiotics.

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