In order to understand the principles behind antimicrobial resistance, it is important to first have a good foundation regarding some key pharmacological concepts that may be relevant to this phenomenon. Presented in this module are topics on the birth and development of our antibiotic arsenal, some basics regarding how antibiotics work and how they are applied for use in veterinary practice, and lastly, how these should be prudently utilized in animals. Knowledge on these basic properties of antibiotics will serve as guidelines for chemotherapy, including appropriate selection and other measures for mitigating antibiotic resistance.

Module Objectives:

This module aims to introduce the students to selected pharmacologic concepts related to antimicrobial resistance. In particular this module will discuss:

1. antibiotic discovery and development;
2. antibiotic activity, effects and modes of action;
3. therapeutic and non-therapeutic antibiotic usage and application in animals; and
4. prudent use of antibiotics in animals.

Pharmacology Module Outline

ANCIENT TIMES

First Treatments

Many ancient cultures used molds, soil, and plants to treat bacterial infections. In Ancient Serbia, China and Greece, old moldy bread was pressed against wounds to prevent infection. In Egypt, crusts of moldy wheaten bread were applied on pustular scalp infections and "medicinal earth" was dispensed for its curative properties[15].

At around 1550 BC, Egyptians have been recorded to use a concoction of honey, lard and lint for dressing wounds. We now know that honey actually contains substantial amounts of hydrogen peroxide which can kill bacteria.

More than 2,000 years ago, moldy bread was used in China, Greece, Serbia, Egypt and probably other ancient civilizations as treatment for some disease conditions, particularly infected wounds. The observed curative powers may have been due to some raw forms of antibiotics produced by the mold growing on the bread.

These remedies were believed to influence the spirits or the gods responsible for illness and suffering. Today we know that the occasional efficacy of these early treatments was due to the active metabolites and chemicals present in these concoctions.

The Advent of Patented Potions

Probably owing to the dramatic impact of infectious diseases and the lack of any other available effective cures, people living before the antibiotic era began often relied on a variety of largely untested remedies to treat their illnesses. These remedies were of highly variable efficacy and safety, and sometimes had no bearing in the cure or relief from disease conditions, but were nonetheless patented and utilized by desperate people with no other alternatives.

Godfrey's Cordial (also called Mother's Friend) and Dalby's Carminative were among the most widely used patent medicines given to infants and children in England and the United States during the latter years of the 18th and early part of the 19th centuries. Both preparations were used-almost always without a physician's advice for a wide variety of symptoms ranging from run of-the mill fretfulness and colic, to the severest forms of dehydration caused by explosive, bloody diarrhea.

Despite their innocuous names, they were sinister preparations because of their opium content; Godfrey's Cordial contained one grain of opium in each two ounces; Dalby's Carminative contained 3ı grain of opium in the same amount. As a result many infants died of opium poisoning during this time (T.E.C. Jr., 1970 "What Were Godfrey's Cordial and Dalby's Carminative?" Pediatrics 45:1011)

Egyptian Papyrus

The Eber's papyrus, which dates back from about 1550 B.C., is the oldest preserved medical document. It contains a list of formulas and remedies to cure illnesses and afflictions ranging from pains to cancer11.

Historical Bacterial Disease Outbreaks

Past civilizations were constantly confronted with fatal infectious diseases, some in catastrophic proportions. Examples of bacterial diseases that have wreaked havoc to humanity are: Black death or plague, cholera and syphilis. If antimicrobials had been available, mankind's history would have been altogether different.

PRE-ANTIBIOTIC ERA

Weapons against bacterial diseases improved just before the turn of the 20th century. The advent of the germ theory of disease, which proposed that microorganisms are the causes of many diseases, caused a revolutionary change in the understanding of the vital role of microbes in infectious diseases. Specific microbial pathogens were identified as the causative agents of many diseases, and a race immediately began to find effective means to kill these implicated microbes.

The first recorded microbial by-product shown to have antimicrobial activity was the blue pigment from *Bacillus pyocyaneus* (now *Pseudomonas aeruginosa*) which stopped the growth of some kinds of bacteria in the test tube. This was serendipitously observed by E. de Freudenreich (Germany) in 1888. Rudolf Emmerich and Oscar Loew (Germany), who later named the substance "**pyocyanase**", performed clinical trials in 1889 showing some effectiveness against many of the infectious diseases of that time. This understandably raised excitement in the scientific community, however, this compound's instability and inherent toxicity in patients later made it clear that pyocyanase had no real clinical application, and thus its popularity eventually declined[16].

Another German physician, named Paul Ehrlich, tirelessly searched for a "magic bullet" that could selectively kill microorganisms. After several failures, in 1910 he finally came up with an arsphenamine chemical dye they referred to as compund 606 and later named **Salvarsan** - the first chemical compound shown to cure a human disease, syphilis [22, 25, 28].

Alexander Fleming, more notable for his discovery of penicllin in the later years, reported in 1920 of a naturally occurring antibacterial substance in human tears that causes lysis in some bacterial cells. He later called this **lysozyme**. Unfortunately, this too did not realize clinical application because of its limited effect on mostly non-pathogenic bacteria, and because it could not be produced in quantities large enough for further trials[12,16].

Dr. Ehrlich

Dr. Ehrlich set aim to find "magic bullets" specific substances which have specific affinities for pathogenic organisms at which they were aimed.

To achieve this, Ehrlich and his assistants tested hundreds of chemical substances. Ehrlich's 606th preparation of an arsenobenzene compund was previously set aside in 1907 as being ineffective. But when Ehrlich asked a Japanese colleague named Hata, who had succeeded in infecting rabbits with syphilis, to test this discarded drug on these rabbits, they found that it was very effective. Thus came the birth of the first chemotherapeutic agent, later named Salvarsan.

The impact of Dr. Ehrlich's contribution to medicine can be best appreciated in the fact that his story was immortalized in a 1940 Warners Bros. movie entitled "Dr. Ehrlich's Magic Bullet".

GOLDEN AGE OF ANTIBACTERIALS

In 1928, **Fleming's** major medical breakthrough came about as he serendipitously discovered penicillin, later to be claimed as the miracle drug of the 20th century. However, the impact of this discovery was not realized until the 1940s, when its applicability as a therapeutic agent was made possible by **Florey and Chain.** Blamed for this delay was the lack of biochemical and microbiological expertise at that time, as well as the lack of interest and support from the scientific community brought about by previous experience with the failure of pyocyanase and the toxicity of Salvarsan.

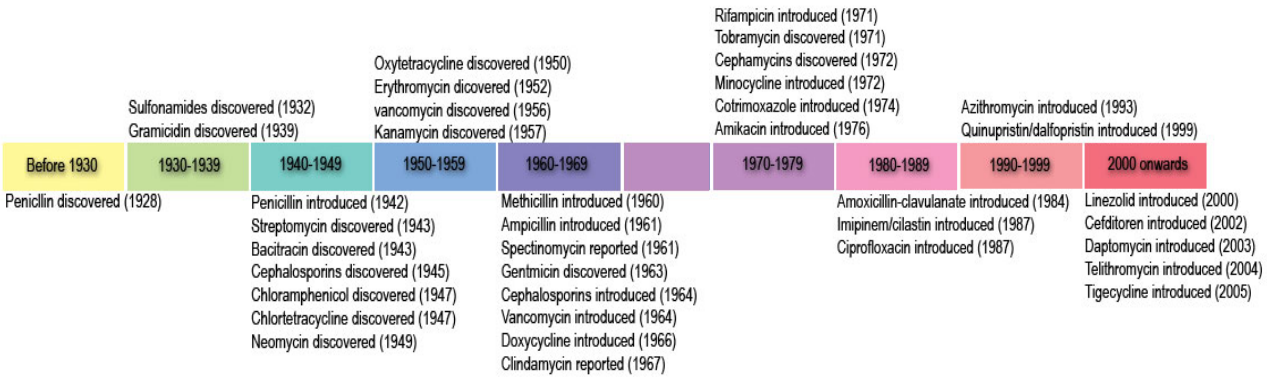
Domagk thought that because dyes have affinity for bacterial cells, they may possibly alter their growth once taken inside. He tested the synthetic newly patented red dye, Prontosil. Luckily, he also tested this chemical in mice; if he relied on test tubes alone, no activity would have been observed and the discovery would have not been made. This is because the active component of the dye, the sulfonamide requires release during a necessary metabolic processes *in vivo*[16].

The first to receive this was drug his own young daughter. A needle was accidentally embedded in her wrist bone, eye first, and broke off when she fell from the stairs. It was surgically removed but a secondary streptococci infection, which Domagk himself identified, resulted in a life-threatening fever. Left with very little option, he asked permission from the attending doctor to give her Prontosil. His daughter recovered almost immediately[20].

For this monumental discovery, Domagk was awarded the 1939 Nobel Prize in Physiology or Medicine, but, being a German national, was forbidden by the Nazi regime to receive it. He was instead arrested and jailed. He finally received the award in 1947, after the war.

In 1935, a breakthrough that ushered the era of antibacterials was made by the German biochemist **Gerhard Domagk** at the Bayer Laboratories of the I.G. Farben company in Germany[19]. He discovered and developed the first **sulfonamide**, a synthetic red dye more popularly known by its trade name of Prontosil, the first commercially available antibacterial. Impressive clinical successes resulted in a sharp decline in mortaliy due to killer diseases such as meningitis, child bed fever and pneumonia. Domagk's discovery saved many lives, including prominent figures such as Winston Churchill6 and Franklin D. Roosevelt, Jr., son of then US President Roosevelt.

Inspired by the groundbreaking work of Domagk (with sulfa) and Fleming, Florey and Chain (with Penicllin), a number of subsequent antimicrobial discoveries quickly followed. To this day, newer antimicrobial compounds continue to be discovered and introduced, although the rate has slowed considerably.



The Penicillin Story

One morning in September 1928, Sir Alexander Fleming who just got back from a holiday, returned to a lab full of contaminated and overgrown plates of staphylococci. While decontaminating the old plates, he noticed some inhibition of bacterial growth around a mold contaminant and took interest because his previous works have been on finding effective antibacterial agents. He later identified the mold as Penicillium spp/, named the extract as penicillin, and published his findings in British Journal of Experimental Pathology in 1929.

After realizing the inherent difficulty in cultivating the mold and purifying the active agent, he thought this disco very had little application.

However, about nine years later, pharmacologist Howard Florey and biochemist Ernst Boris Chain read his work and took interest in exploring it furher chemically. They later successfully achieved purification and large-scale production of the first antibiotic which, after having saved millions of lives since its introduction in 1942, was later acclaimed as the miracle drug of the 20th century. For this notable achievement Fleming, Florey and Chain shared the Nobel Prize for Physiology and Medicine in 1945.

POST GOLDEN AGE

Just a few years after the golden age of antimicrobials, warning signs of developing resistance were observed. It has now become clear that microorganisms are countering the impact of antimicrobial resistance at an often alarming speed. More and more bacteria with multiple drug resistance are also being observed. Although still surrounded by a number of controversies and debates as to the nature and gravity of this resistance phenomenon, various reports support the contention that the abuse and misuse of antibiotics is largely responsible for the developing resistance problem[1, 13, 17, 18, 26].


ALEXANDER FLEMING

Based on his laboratory observations, the famed penicillin discoverer Alexander Fleming had predicted in 1945 that misuse of this discovery could lead to the election and propagation of mutant forms of bacteria resistant to the drug. He warned that too small doses that fail to completely clear the infection would breed microbes trained to resist the drug, which could then eventually be passed on to other susceptible individuals. Against this warning, penicillin was eventually made freely available to the public, driven by the public clamor for this "miracle drug" and the business opportunities that came along with this medical breakthrough. Various preparations of salves, lonzenges, nasal ointments and even cosmetic creams were sold over-the-counter. And true enough, as Fleming correctly foretold, bacterial resistance to penicillin slowly but steadily built up over the years, to the point that by 1955, most countries restricted the use of penicillin as "by prescription" only. However, the uncontrolled usage was already widespread, and so is the observed resistance in several bacterial pathogens, particularly staphylococci..

A concerted effort was exerted by pharmaceutical companies to thwart this resistance, which eventually led to the discovery and introduction in the early 1960s of a semisynthetic penicillin, called methicillin, which was insensitive to the bacterial enzymes that degrade penicillin. Although this seemed to have initially controlled penicillin resistance in the years that followed, the subsequent emergence of resistance to methicillin, such as that seen in methicillin resistant Staphylococcus aureus (MRSA), is now a current problem faced in hospitals worldwide.

This resistance phenomenon is not restricted to penicillin alone. The same was observed for the other antibiotics which were subsequently discovered and made commercially available to the public in the latter half of the 20th century. In the recent years, this was made even more complicated by the fact that the observed development of antimicrobial resistance has superseded the pace at which discoveries and development of better antibiotic treatments are made. It is feared that if this is not addressed properly in time, the world will be back to the pre-antibiotic era when currently treatable infectious conditions such as pneumonia, diarrhea, or even wound infections, will eventually be considered as life-threatening due to the lack of available effective treatment in the medical arsenal. This has become one of the major medical issues of concern in the 21st century.

The advent of molecular biological approaches proved that, resistance genes are also horizontally transferred among bacteria at a rate that was greater than previously expected. This poses a grim scenario for the generation to come when most antimicrobials might no longer be effective, bringing human and veterinary medicine back again to the pre-antibiotic era where common bacterial infections could once more prove lethal.

Not losing hope, the fight against microbes continues. Several government agencies, international groups, pharmaceutical industries and other stakeholders in various countries and continents continue to work to mitigate further emergence and spread of antimicrobial resistance genes. Alternative drugs are being explored, some antimicrobials have been banned for use in food animals and regulations such as those requiring antimicrobial prescriptions are often used to promote appropriate use for both people and animals. Worldwide, health professionals are being re-educated about the responsible and judicial use of antimicrobials.

INTRODUCTION

The word **antimicrobial** was derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms. This is not synonymous with antibiotics, a similar term derived from the Greek word anti (against) and biotikos (concerning life). By strict definition, the word "**antibiotic**" refers to substances produced by microorganisms that act against another microorganism. Thus, antibiotics do not include antimicrobial substances that are synthetic (sulfonamides and quinolones), or semisynthetic (methicillin and amoxicillin), or those which come from plants (quercetin and alkaloids) or animals (lysozyme).

In contrast, the term "antimicrobials" include all agents that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal).
Notice that the term "antibacterials", being the largest and most widely known and studied class of antimicrobials, is often used interchangeably with the term "antimicrobials" and will be the major focus of this website.

Antibiotics Versus Antimicrobials

An **ANTIBIOTIC** is a low molecular substance produced by a microorganism that at a low concentration inhibits or kills other microorganisms.

An **ANTIMICROBIAL** is any substance of natural, semisynthetic or synthetic origin that kills or inhibits the growth of microorganisms but causes little or no damage to the host.
All antibiotics are antimicrobials, but not all antimicrobials are antibiotics.

CLASSIFICATION OF ANTIBACTERIAL AGENTS

Antimicrobials are classified in several ways, including:

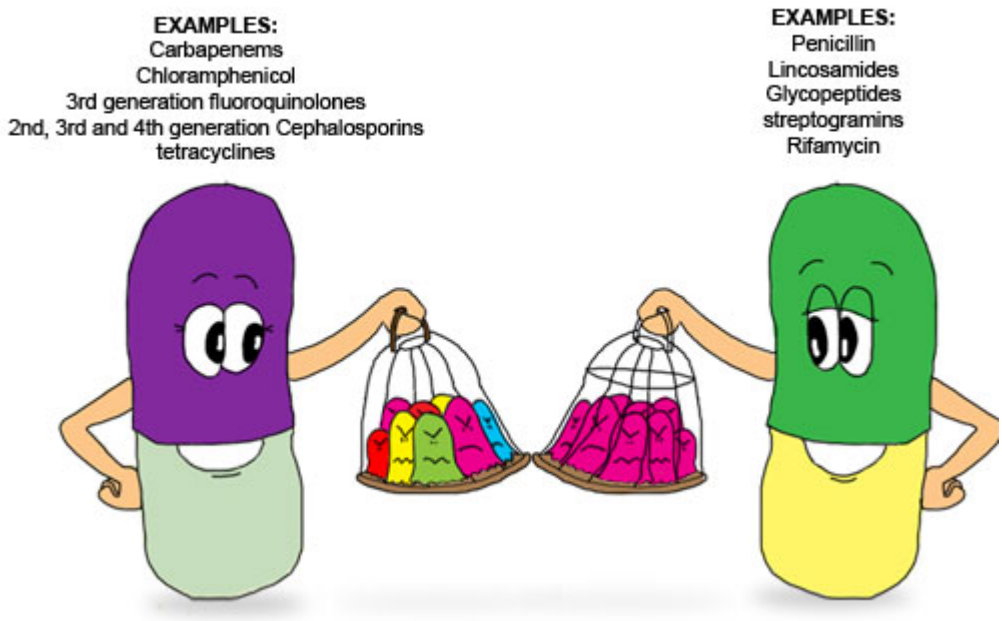
1. spectrum of activity
2. effect on bacteria
3. mode of action

CLASSIFICATION ACCORDING TO SPECTRUM OF ACTIVITY.

Depending on the range of bacterial species susceptible to these agents, antibacterials are classified as broad-spectrum, intermediate-spectrum, or narrow- spectrum. Note that the spectra of activity may change with acquisition of resistance genes, as will be discussed in the next module.

1. **Broad spectrum antibacterials** are active against both Gram-positive and Gram-negative organisms. Examples include: tetracyclines, phenicols, fluoroquinolones, “third-generation” and “fourth-generation” cephalosporins.

2. **Narrow spectrum antibacterials** have limited activity and are primarily only useful against particular species of microorganisms. For example, glycopeptides and bacitracin are only effective against Gram-positive bacteria, whereas polymixins are usually only effective against Gram negative bacteria. Aminoglycosides and sulfonamides are only effective against aerobic organisms, while nitroimidazoles are generally only effective for anaerobes.



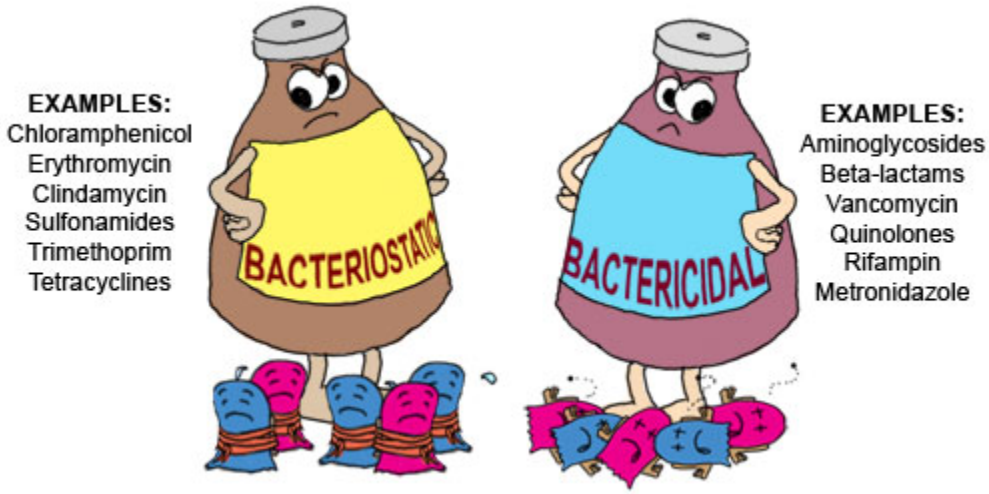
Clinical Implications: Intrinsic Resistance

Knowledge of the intrinsic resistance of a pathogen of concern is important in practice to avoid inappropriate and ineffective therapies.

For bacterial pathogens which are naturally insensitive to a large number of classes of antimicrobials, such as Mycobacterium tuberculosis and Pseudomonas aeruginosa, this consideration can pose a limitation in the range of options for treatment and thus consequently further increase the risk for emergence of acquired resistance.

EFFECT ON BACTERIA

Because of differences in the mechanisms by which antibiotics affect bacteria, the clinical use of antibacterials may have very different effects on bacterial agents, leading to an endpoint of either inactivation or actual death of the bacteria.



1. **Bactericidal drugs** are those that kill target organisms. Examples of bactericidal drugs include aminoglycosides, cephalosporins, penicillins, and quinolones.

2. **Bacteriostatic drugs** inhibit or delay bacterial growth and replication. Examples of such include tetracyclines, sulfonamides, and macrolides.

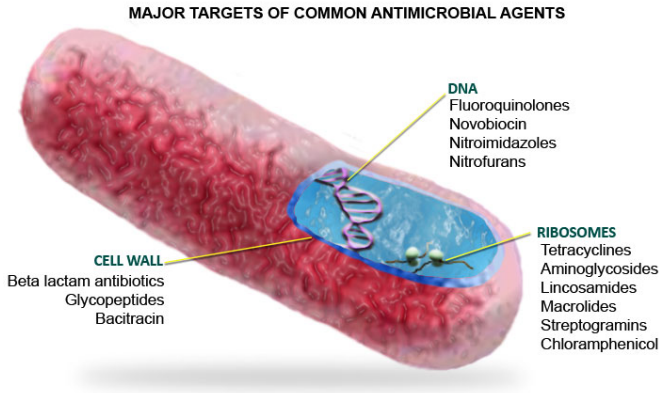
Some antibiotics can be **both bacteriostatic and bactericidal**, depending on the dose, duration of exposure and the state of the invading bacteria. For example, aminoglycosides, fluoroquinolones, and metronidazole exert concentration-dependent killing characteristics; their rate of killing increases as the drug concentration increases.

Clinical Implications: Bacteriostatic Vs. Bactericidal Antibacterials

Onset of action for bacteriostatic agents is generally slower than that of bactericidal agents. In addition, bacteriostatic drugs require a working immune system for effective elimination of the microorganism by the infected host. Bacteriostaic antibiotics are therefore not advisable for use in animals with immunosuppressed or immunocompromised conditions and those suffering from life-threatening acute infections.

MODE OF ACTION

Different antibiotics have different modes of action, owing to the nature of their structure and degree of affinity to certain target sites within bacterial cells.



1. **Inhibitors of cell wall synthesis**. While the cells of humans and animals do not have cell walls, this structure is critical for the life and survival of bacterial species. A drug that targets cell walls can therefore selectively kill or inhibit bacterial organisms. Examples: penicllins, cephalosporins, bacitracin and vancomycin.

2. **Inhibitors of cell membrane function**. Cell membranes are important barriers that segregate and regulate the intra- and extracellular flow of substances. A disruption or damage to this structure could result in leakage of important solutes essential for the cell's survival. Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorly selective and can often be toxic for systemic use in the mammalian host. Most clinical usage is therefore limited to topical applications. Examples: polymixin B and colistin.

3. **Inhibitors of protein synthesis**. Enzymes and cellular structures are primarily made of proteins. Protein synthesis is an essential process necessary for the multiplication and survival of all bacterial cells. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria, and consequently leads to the death of the organism or the inhibition of its growth and multiplication. Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, tetracyclines.

4. **Inhibitors of nucleic acid synthesis**. DNA and RNA are keys to the replication of all living forms, including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: quinolones, metronidazole, and rifampin.

5. **Inhibitors of other metabolic processes**. Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. Sulfonamides target and bind to dihydropteroate synthase, trimethophrim inhibit dihydrofolate reductase; both of these enzymes are essential for the production of folic acid, a vitamin synthesized by bacteria, but not humans.

INHIBITORS OF CELL WALL SYNTHESIS

BETA LACTAM ANTIBIOTICS	
Mode of action:	*Inhibition of cell wall synthesis.* This particular group is characterized by its four-membered, nitrogen-containing beta-lactam ring at the core of its structure, which is key to the mode of action of this group of antibiotics. Beta lactam antibiotics target the penicillin-binding proteins or PBPs - a group of enzymes found anchored in the cell membrane, which is involved in the cross-linking of the bacterial cell wall. The beta-lactam ring portion of this group of antibiotics binds to these different PBPs, rendering them unable to perform their role in cell wall synthesis. This then leads to death of the bacterial cell due to osmotic instability or autolysis.
Examples:	**Penicllins**: NATURAL: penicillin G, penicillin V; PENICILLINASE-RESISTANT PENICILLLIN: methicillin; oxacillin, nafcillin; EXTENDED SPECTRUM PENICILLIN: ampicillin, amoxicillin, carbenicillin **Cephalosporins**: cephalothin; cefamandole, cefotaxime **Carbapenems:** primaxin **Monobactams:** aztreonam
Source:	**Penicillin**: *Penicillum chrysogenum (*syn: *P. notatum), Aspergillus nidulans* **Cephalosporin:** *Acremonium chrysogenum* (syn: *Cephalosporium acremonium), Paecilomyces persinicus, Streptomyces clavuligerus, Nocardia lactamdurans, Flavobacterium* sp. *Lysobacter lactamgenus*
Spectrum of activity:	Broad-spectrum: carbapenems, 2nd, 3rd and 4th generation cephalosporins Narrow-spectrum: penicillin, 1st generation cephalosporins, monobactams
Effect on bacteria:	Generally bactericidal
Examples of applications in Veterinary Medicine:	**Ruminants**: Anthrax, listeriosis, leptospirosis, clostridial and corynebacterial infections; streptococcal mastitis, keratoconjunctivitis **Swine:** erysipelas, streptococcal and clostridial infections **Horses**: Tetanus, strangles, other strep and clostridial infections, foal pneumonia, **Dogs and cats:** streptococcal and clostridial infections, UTI **Poultry**: Necrotic enteritis, ulcerative enteritis, and intestinal spirochetosis
Miscellaneous:	Although beta – lactam antibiotics should theoretically work against all types of bacteria, this is not the case. This is because different bacteria have varying PBP content and nature. Also, some bacteria have natural structural characteristics which do not favor this mode of action (e.g., Gram-negatives have an outer membrane layer which makes the PBPs more difficult to reach).

GLYCOPEPTIDES	
Mode of action:	*Inhibition of cell wall synthesis.* Glycopeptides bind to precursors of cell wall synthesis which leads to interference of the penicillin-binding protein (PBP) enzymes, such as transpeptidases, to incorporate the precursors into the growing cell wall. With this, cell wall synthesis stops and cell death often follows.
Example:	Vancomycin, teicoplanin, avoparcin
Source:	*Various species of actinomycetes such as* Streptomyces orientalis *(vancomycin),* Nocardia actinoides *(Actinoidin)*
Spectrum of activity:	Narrow spectrum affecting only Gram-positive bacteria
Effect on bacteria:	Bactericidal
Examples of applications in Veterinary Medicine:	**Vancomycin:** “Last resort” drug in human medicine with very few applications in animals. **Avoparcin:** Previously used extensively for growth promotion of chickens and pigs in some countries
Miscellaneous:	Ristocetin, although also bactericidal like vancomyin, was discontinued for use as an antibiotic because it causes aggregation of blood platelets. However, this unfavorable attribute was put to good use in helping to diagnose von Willebrand’s disease. Some glycopeptides like avoparcin, A-4696 or actaplanin and A35512 are being marketed and used as feed additive in some countries. When it became apparent that avoparcin selected for VRE (vancomycin resistant enterococci) in animals, Denmark and subsequently all of Europe withdrew it from animal feeds to reduce risk for humans. The ban in Denmark was reportedly followed by an immediate decrease in VRE isolates in poultry, but not in pigs, until tylosin was also banned from use in feed (Aarestrup *et al.,* 2001).

INHIBITORS OF CELL MEMBRANE FUNCTION

POLYMIXINS	
Mode of action:	*Inhibition of cell membrane function*. Disrupt the structure of cell membrane phospholipids and increase cell permeability by a detergent-like action, causing cell death. This binding is competitive with calcium and magnesium. Polymixins have also been shown to neutralize endotoxins.
Example:	Polymixin B, colistin (Polymixin E)
Source:	*Bacillus polymyxa*
Spectrum of activity:	Narrow spectrum affecting primarily Gram-negative bacteria
Effect on bacteria:	Bactericidal
Examples of applications in Veterinary Medicine:	**Cattle:** colibacillosis and salmonellosis in calves, mastitis **Swine:** neonatal porcine colibacillosis **Horses:** bacterial keratitis or metritis caused by *Klebsiella* spp. **Dogs and cats:** bacterial keratitis, otitis externa, skin infections
Miscellaneous:	Polymixins are not absorbed from the gastrointestinal tract. Because of their excessive nephrotoxic nature, other polymixin classes have been discarded.

INHIBITORS OF PROTEIN SYNTHESIS

AMINOGLYCOSIDES	
Mode of action:	*Inhibition of protein synthesis.* Once inside the bacterial cell, aminoglycosides bind to the 30s ribosomal sub-unit and cause a misreading of the genetic code. This subsequently leads to the interruption of normal bacterial protein synthesis.
Example:	Gentamicin, tobramycin, amikacin, streptomycin, kanamycin, neomycin
Source:	*Streptomyces* spp. *Microsmonospora* spp.
Spectrum of activity:	Broad-spectrum but NOT effective against anaerobic bacteria
Effect on bacteria:	Bactericidal (dose dependent)
Examples of applications in Veterinary Medicine:	Due to its toxicity, aminoglycoside use has been clinically limited to severe infections. The more toxic antibiotics in this class have been restricted to topical or oral use for the treatment of infections caused by Enterobacteriaceae. The less toxic aminoglycosides are used for parenteral treatment of severe sepsis caused by Gram-negative aerobes.
Miscellaneous:	Nephrotoxic and ototoxic; not effective against anaerobic bacteria.

CHLORAMPHENICOL	
Mode of action:	*Inhibition of protein synthesis,* Chloramphenicol irreversibly binds to a receptor site on the 50S subunit of the bacterial ribosome, inhibiting peptidyl transferase. This inhibition consequently results in the prevention of amino acid transfer to growing peptide chains, ultimately leading to inhibition of protein formation.
Spectrum of activity:	Broad-spectrum

Effect on bacteria:	Bacteriostatic
Examples of applications in Veterinary Medicine:	Because of its capacity to cause fatal aplastic anemia in humans, chloramphenicol is prohibited in food animals in the U.S. and many countries. May be considered for some anaerobic infections in companion animals, such as serious ocular infections, prostatitis, otitis media/interna and salmonellosis.
Miscellaneous:	Causes bone marrow depression and may compromise antibody production if given prior to vaccination. Anaphylaxis, vomiting and diarrhea have been reported in dogs and cats. Cats are more likely to be susceptible to toxicity.

TETRACYCLINES	
Mode of action:	*Inhibition of protein synthesis.* Once tetracyclines have been transported into the cell, this class of antibiotic reversibly binds to receptors on the 30S ribosomal subunit of the bacteria, preventing attachment of aminoacyl-tRNA to the RNA-ribosome complex. This prevents the addition of amino acids to the elongating peptide chain, preventing synthesis of proteins.
Example:	Chlortetracycline, oxytetracycline, demethylchlortetracycline, rolitetracycline, limecycline, clomocycline, methacycline, doxycycline, minocycline
Source:	*Streptomyces* spp.; some are also semi-synthetic
Spectrum of activity:	Broad-spectrum. Exhibits activity against a wide range of Gram-positive, Gram-negative bacteria, atypical organisms such as chlamydiae, mycoplasmas, rickettsiae and protozoan parasites.
Effect on bacteria:	Bacteriostatic
Examples of applications in Veterinary Medicine:	Tetracyclines are primarily indicated in the treatment of borreliosis, brucellosis (usually in combination with rifampin or streptomycin), chlamydiosis, ehrlichiosis, leptospirosis, listeriosis, rickettsiosis, and tularemia.
Miscellaneous:	Tetracyclines have also been used for non-antibacterial purposes, having shown properties such as anti-inflammatory activity, immunosuppresion, inhibition of lipase and collagenase activity, and wound healing.

MACROLIDES	
Mode of action:	*Inhibition of protein synthesis.* Macrolides reversibly bind to 50S subunit of the ribosomes and inhibit transpeptidation and translocation processes, resulting in premature detachment of incomplete polypeptide chains.
Examples:	Macrolides approved for veterinary use: Erythromycin, Tylosin, Spiramycin, Tilmicosin, Tulathromycin
Source:	*Saccharopolyspora erythaea* (Erythromycin) *Streptomyces fradiae* (Tylosin) Some are semisynthetic (Tilmicosin, Tulathromycin)
Spectrum of activity:	Narrow-spectrum
Effect on bacteria:	Generally bacteriostatic, but may be bactericidal at high concentrations or against low numbers of a highly susceptible bacterial organism.
Examples of applications in Veterinary Medicine:	**Erythromycin** – drug of choice against *Campylobacter jejuni*. Can be an alternative to penicillin in penicillin-allergic animals and second choice for anaerobic infections. **Tylosin and spiramycin** – used against *Mycoplasma* infections; used as growth promotants. **Tilmicosin** – against *Mannheimia, Actinobaciullus, Pasteurella, Mycoplasma;*
Miscellaneous:	Parenteral use of tylosin in horses has been fatal, while oral administration has no indication for use and might result in enterocolitis. Tilmicosin can be fatal to pigs if given parenterally, and is not recommended for use in goats due to toxicity.

LINCOSAMIDES	
Mode of action:	*Inhibition of protein synthesis.* Lincosamides bind to the 50S ribosomal subunit and inhibit peptidyl transferases.
Example:	Lincomycin, Clindamycin and Pirlimycin
Source:	*Streptomyces lincolnensis* subsp. *lincolnensis*
Spectrum of activity:	Moderate-spectrum; they are primarily active against Gram-positive bacteria, most anaerobic bacteria and some mycoplasma.
Effect on bacteria:	Can be bactericidal or bacteriostatic, depending on the drug concentration, bacterial species and concentration of bacteria.
Examples of applications in Veterinary Medicine:	❑ **General:** clindamycin has an excellent activity against anaerobes; ❑ **Swine:** lincomycin is used extensively in the prevention and treatment of dysentery and sometimes in mycoplasma infections. ❑ **Cattle:** used as intramammary infusion in mastitis (pilrimycin); ❑ **Horses:** should not be used in horses; ❑ **Dogs and cats:** for infections with Gram-positive cocci and anaerobes ❑ **Poultry:** for the control of mycoplasmosis (usually in combination with spectinomycin) and necrotic enteritis.
Miscellaneous:	Should not be used in horses due to their potential to cause fatal enterocolitis.

STREPTOGRAMINS	
Mode of action:	*Inhibition of protein synthesis.* Streptogramins irreversibly bind to the 50S ribosomal subunit. Group A streptogramins prevent peptide bond formation during chain elongation step, while group B components cause the release of incomplete peptide chains from the 50S ribosomal subunit.
Example:	Virginiamycin
Source:	*Streptomyes virginiae*.
Spectrum of activity:	Narrow spectrum; mainly Gram-positive bacteria
Effect on bacteria:	Group A OR Group B – Bacteriostatic Group A AND Group B - Bacteriocidal
Examples of applications in Veterinary Medicine:	Used largely as a growth promotant for livestock, but has also been used to prevent laminitis in horses.
Miscellaneous:	Virginiamycin has been developed largely as a growth promotant and is still used in many countries. It has been banned by the European Union since 1999.

INHIBITORS OF NUCLEIC ACID SYNTHESIS

FLUOROQUINOLONES	
Mode of action:	*Inhibition of nucleic acid synthesis.* Fluoroquinolones have been shown to bind to the DNA gyrase-DNA complex and interrupt a process that leads to the negative supercoiling of bacterial DNA. This disruption leads to defects in the necessary supercoiling, and render the bacteria unable to multiply and survive.
Example:	Enrofloxacin, ciprofloxacin, Danofloxacin, Difloxacin, Ibafloxacin, Marbofloxacin, Pradofloxacin, Orbifloxacin
Source:	Synthetic
Spectrum of activity:	Broad-spectrum – 3rd generation fluoroquinolones Narrow-spectrum – other fluoroquinolones
Effect on bacteria:	Bactericidal
Examples of applications in Veterinary Medicine:	**Ruminants –** acute respiratory disease, infections with *E. coli, Salmonella, Mycoplasma,* mastitis, metritis, conjunctivitis. **Swine –** treatment of infections caused by *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae, E. coli,* and *Pasteurella multocida.* Should never be administered in feeds because residues can contaminate the environment; prohibited for use in pigs in some countries. **Horses –** for infections with bacteria resistant to the first drug of choice; not recommended in young growing horses (may cause cartilage erosion). **Dogs and Cats –** prostatitis, mastitis, rhinitis, pyoderma, otitis, wound infections, peritonitis, osteomyelitis, and soft tissue infections; not recommended for use in animals less than eight months of age (or <18 months of age for large breed dogs to avoid arthropathoc effects).
Miscellaneous:	Available formulations and/or approved use in different animal species vary widely between countries; some extra-label use, but may be prohibited in some countries.

RIFAMYCINS	
Mode of action:	*Inhibition of nucleic acid synthesis.* Enters neutrophils and macrophages and inhibits DNA-dependent RNA polymerase in bacteria
Example:	Rifampin, Rifabutin, Rifapentine
Source:	*Amycolaptosis mediterrainei*
Spectrum of activity:	Broad-spectrum; also has antiviral and antifungal activity
Effect on bacteria:	Bactericidal
Miscellaneous:	Rifampin is used as a first line oral drug treatment for tuberculosis in humans.

INHIBITORS OF METABOLIC PROCESSES

SULFONAMIDES	
Mode of action:	*Inhibition of other metabolic processes*. Sulfonamides interfere with folic acid synthesis by preventing addition of para-aminobenzoic acid (PABA) into the folic acid molecule through competing for the enzyme dihydropteroate synthetase.
Example:	Sulfadiazine, sulfamethoxazole, sulfadoxine
Source:	Synthetic
Spectrum of activity:	Broad-spectrum; affects Gram-positive and many Gram-negative bacteria, toxoplasma and protozoal agents
Effect on bacteria:	Bacteriostatic
Miscellaneous:	Act synergistically (and becomes bactericidal) in combination with diaminopyrimidines (trimethoprim)

DIAMINOPYRIMIDINES (TRIMETHOPRIM)	
Mode of action:	*Inhibition of other metabolic processes*. Trimethoprim interferes with the folic acid pathway by binding the enzyme dihydrofolate reductase.
Example:	Trimethoprim, Aditoprim, Baquiloprim, Ormetoprim
Source:	Synthetic
Spectrum of activity:	Broad-spectrum; affects Gram-positive and many Gram-negative bacteria
Effect on bacteria:	Bacteriostatic
Miscellaneous:	Act synergistically (and becomes bactericidal) in combination with sulfonamides

INTRODUCTION

The use of antimicrobials in animals closely parallels their discovery and usage in humans. Sulfonamide was the first antimicrobial to be introduced to food animal medicine in the 1940s. The subsequent discoveries and availabilities of newer antibiotics in the early 50's quickly led to their widespread therapeutic usage for a multitude of infectious diseases in virtually all food animal species. Antibiotics are also given to food animals for growth promotion and prophylactic medication, which are discussed in the species specific sections of this website.

The introduction and use of antimicrobials in animals has brought major benefits to both animals and humans. Some of these benefits are:

1. Reduction of animal pain and suffering;
2. Protection of livelihood and animal resources;
3. Assurance of continuous production of foods of animal origin;
4. Prevention or minimizing shedding of zoonotic bacteria into the environment and the food chain;
5. Containment of potentially large-scale epidemics that could result in severe loss of animal and human lives.

Clearly, the advantages generated by the use of antimicrobials for food animals transcends more than just the well-being of the animals, as it has also brought about economic benefits for the food animal producers and a more secured and safer health for the general public. However, there are conflicting opinions regarding the proper role of antimicrobials in the production of poultry and livestock. Many believe that the current scientific evidence sufficiently supports a curtailment of current U.S. antibiotic usage practices because they may pose a serious risk to both animal and human health through ever increasing rates of antimicrobial resistance. Others argue that current U.S. regulatory policies regarding antibiotic usage are appropriate, and that further curtailment in antibiotic usage for food animals would be economically harmful to both consumers and producers, and quite unnecessary given the ill-defined risks of inducing greater rates of antimicrobial resistance. One thing, upon which all can all agree, is that the unnecessary or wasteful use of antibiotics should be curtailed when non-antibiotic solutions are readily available or when the use of antibiotics for a particular disease condition are clearly not efficacious. It is upon this common ground that the human medical and veterinary medical communities call for the proper and prudent use of antibiotics, and mandate the proper training of human and animal health professionals regarding the judicious, proper and non-wasteful use of all antibiotics.

THERAPEUTIC USE OF ANTIBIOTICS IN ANIMALS

Therapeutic use of antibiotics refers to their use to treat clinically ill animals. Although the importance of good management and preventive medicine should not be underestimated, there are many disease conditions in animals that can only be addressed by antimicrobial therapy. Therapeutic use of antibiotics in animals is probably a little more complicated than it is for human medicine, given the variations between species and the reasons for which animals are owned and are being treated.

Ideally, antimicrobial susceptibility testing is done to determine the available options for therapy. It is important to note, however, that bacterial susceptibility is not the only consideration when selecting an antibiotic from a range of options. Aside from the susceptibility and species of the invading pathogen, factors to consider in the appropriate selection of antimicrobial therapies should include the drug's attributes (such as pharmacodynamics, pharmacokinetics, toxicity, tissue distribution), the host characteristics (such as age, species, immune status), the accountability to the public and other issues such as cost effectiveness.

Each of these issues is important in making sound decision regarding the advisability of each antimicrobial therapy. Details on each of these considerations, although not covered here, should be further explored.

Some Points to Consider in Making Antibiotic-Related Decisions

TO TREAT OR NOT TO TREAT:

1. Does the condition necessitate treatment?
2. Are there other options besides treatment?
3. Will the potential consequences outweigh the benefit of treatment?
4. What is the host species involved? Is it worth treating?
5. Will treatment work for the pathogen involved?
6. Are there any risks to public health when this is done?

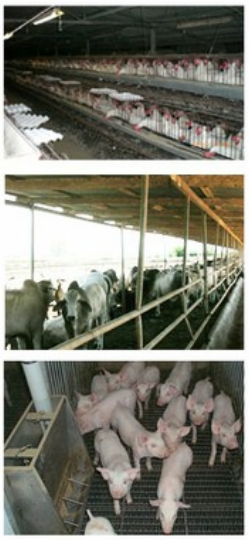
WHEN TREATMENT IS THE BEST OPTION:

1. Which drug would be best against the condition of interest?
2. What is the optimal dosage, duration and route for the drug of choice?
3. Will the drug's attributes work for the current condition at hand?
4. What are the hosts' attributes? Will the drug not put the animals at further risk given these?
5. What are the pathogen's attributes and where is it? Will the drug s gain effective access to it?
6. Will the public be put to further risks with these choices?
7. Will the treatment be cost-effective?

NON-THERAPEUTIC USE OF ANTIBIOTICS IN ANIMALS

The continuously increasing world demand for animal protein has led to increasingly efficient intensive farming systems where animals are raised to maximize the amount of utilizable product at the least cost. High stocking densities and rapid animal growth, coupled with the reduction of available agricultural space, can sometimes facilitate the transmission of infectious agents and the susceptibility of the animals to infectious diseases. It has long been established that antibiotics may help improve production and prevent disease; for this reason, food animal producers utilize antibiotics for non-therapeutic purposes. These uses are generally referred to as non-therapeutic applications of antibiotics; of which there are two main categories:

1. Use of antibiotics in animals for growth promotion
2. Use of antibiotics in animals for metaphylaxis



Unlike in humans, an even larger proportion of antibiotics produced for veterinary use are utilized in animal herds or flocks for purposes other than treatment. A report by the Union of Concerned Scientists estimated that in the United States alone, the livestock producers use about 24.6 million pounds of antimicrobials for non-therapeutic purposes, a volume about eight times greater than the 3 million pounds estimated use for human medicine (Mellon et al., 2001).

NON-THERAPEUTIC USE OF ANTIBIOTICS IN ANIMALS

Use of antibiotics in animals for growth promotion

Antibiotics as growth promoatant was discovered in the 1940s, when it was observed that chicks improve in growth when fed bacterial shells of Streptomyces aureofaciens from which antibiotics had been extracted. Because the amount of antibiotic that can provide growth enhancement was extremely small, the effect was regarded as largely nutritional by producers and authorities in the food industry[16]. In the years to follow, other countries also allowed the use of antibiotics in animal feeds. Subsequently, however, when the emergence of antibiotic resistance was recognized as an increasing risk, the use of growth promoters became the focus of numerous regulatory interventions, and bans on growth promotants were often enacted on particular classes of antibiotics. To date, different countries have different lists of approved and banned growth promoter antibiotics in their respective livestock industries.

HOW DO SUBTHERAPEUTIC LEVELS OF ANTIBIOTICS PROMOTE GROWTH?

Although repeatedly proven in various studies, the mechanism of action for the enhancement of growth of subtherapeutic levels of antibiotics remains unclear. Among the hypotheses tested are the following:

1. Stimulation of intestinal synthesis of vitamins by bacteria.
2. Reduction in total numbers of bacteria in the intestinal tract with a lowering of competition between microorganisms and host animals for nutrients.
3. Inhibition of harmful bacteria which may be mildly pathogenic or toxin-producing.
4. Inhibition of bacterial urease.
5. Improved energy efficiency of the gut.
6. Inhibition of bacterial cholytaurin hydrolase activity.
7. Nutrient sparing.
8. Improved nutrient absorption from morphological changes to small intestinal epithelium.
9. Modification of intestinal enzyme activity.
10. Reduced immune stimulation.
11. Modification of rumen microbial metabolism.

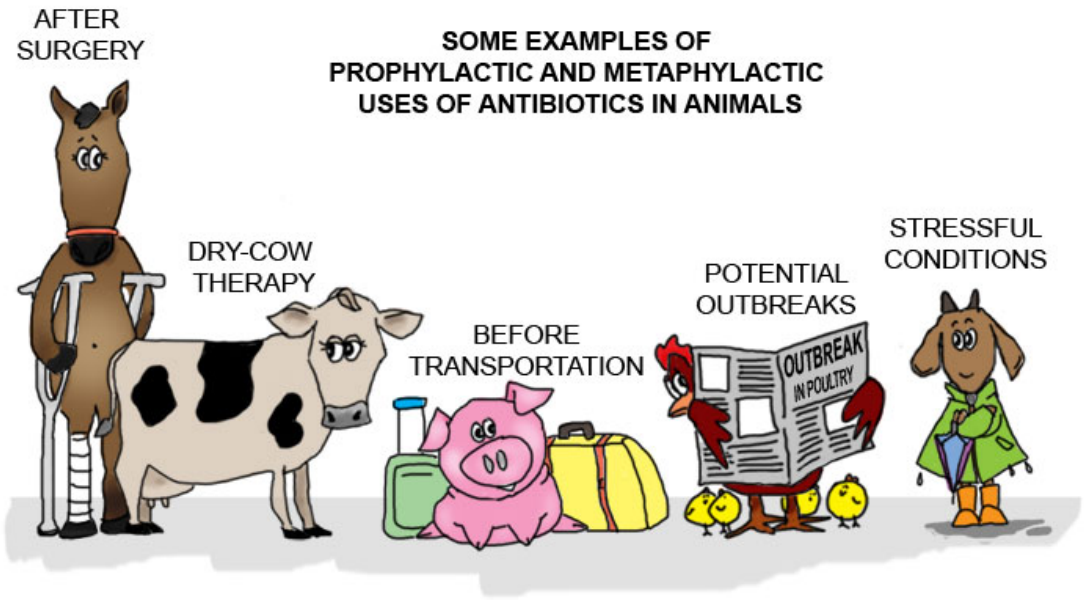
(From Giguere et al., 2006)

ANTIMICROBIAL GROWTH PROMOTANTS

The use of subtherapeutic doses of antibiotics as growth promotants was yet another unintentional discovery. In 1948, animal nutritionist Robert Stokstad and biochemist Thomas Jukes of the Lederle company, were then extensively working on a variety of vitamin B12 which was believed to be the “animal protein factor” that can enhance the growth of chickens. Because the Lederle laboratories (the laboratory where the very first tetracycline, chlortetracycline, was discovered) uses vats of Streptomyces auerofaciens for the production of the antibiotic aureomycin, they utilized its cellular remains after the antibiotic had been extracted because they found that this contain substantial amounts of Vit B12. They found that chicks receiving supplements of S. aureofasciens fermentation grow 24% more rapidly than those receiving liver extract, another source of this vitamin. They later realized that this observed growth enhancement was not because of the vitamin, but due to the minimal residues of antibiotics left in the bacterial carcasses. This opened a whole new market for antibiotics to the multi-billion dollar industry that it is today; a surprising offshoot from the vitamin research that had no direct investment return to the laboratory.

NON-THERAPEUTIC USE OF ANTIBIOTICS IN ANIMALS

Use of Antibiotics in Animals for Prophylactic or Metaphylactic Purposes



It is not uncommon for veterinarians to give antibiotics to animals that are not currently ill with a particular disease, but are at high risk of acquiring an infection. For example, an animal may be treated with antibiotics after having undergone surgery or injurious trauma (**prophylaxis**) or herds and flocks may be given antibiotics if they are at risk of suffering an outbreak of infectious disease due to exposure to disease agents or extremely unfavorable host or environmental conditions (**metaphylaxis**). In companion animal veterinary medicine, antibiotics are commonly used to control secondary bacterial invasions such as during surgical procedures and managing infection-promoting disease conditions such as urolithiasis. In poultry and livestock, mass administration of antibiotics is often practiced when transporting or moving young animals, during dry-cow therapy in dairy cows and in preventing respiratory and intestinal maladies when animals have been subjected to severely stressful conditions.

Prophylactic or metaphylactic use of antibiotics can be a substantial aid in the control and prevention of numerous animal diseases in both food and companion animals. However, this use of antibiotics should never be intended to replace the need for good management practices, given that the use of antibiotics will eventually lead to resistance. As was the case with therapeutic uses of antimicrobials, issues to be considered when deciding whether or not to use an antibiotic include knowledge of the pathogen involved and knowledge of the antibiotic's properties given the species of animal and its intended use for food or companionship.

Prudent use of antimicrobials, which is also referred to as "**judicious use**" or "**antimicrobial stewardship**", is the optimal selection of drug, dose and duration of antimicrobial treatment, along with reduction of the inappropriate and excessive use as a means of slowing the emergence of antimicrobial resistance (Shales et al., 1997 as cited by Weese JS, 2006).

Although this may be more straightforward for human medicine, the nature by which antimicrobials are utilized in animals and the influences of various stakeholders in the standards by which these are raised, make such practice more complicated for veterinary medicine. The prudent use of antimicrobials in veterinary medicine are principled guidelines created to prevent abusive use of antimicrobials in animals, primarily to curb or mitigate the imminent risk of breeding resistant microorganisms unresponsive to currently available chemotherapy in both animals and humans. Veterinarians are on the forefront of upholding such manner of use having dual roles of protecting animals from pain and suffering, while safeguarding the interest of the public health.

More details on antimicrobial practices and prudent use in particular animal species can be found in the modules on clinical applications.

Summary

- The advent of antibiotics revolutionized the means by which infectious diseases were treated. Suddenly, common infections became easily curable and outbreaks of infectious disease were readily controlled. However, the declaration of victory over bacterial pathogens was premature. Antimicrobial resistance quickly emerged to reduce the clinical usefulness of each new antibiotic that was developed. Mitigation of antimicrobial resistance is therefore necessary, and requires that veterinarians and other health professionals understand antibiotic sensitivity and resistance at the population, organism, cellular and molecular levels.

- An antimicrobial is any substance of natural, semisynthetic or synthetic origin that kills or inhibits the growth of microorganisms while hopefully causing minimal damage to the host. Antimicrobials can be used as therapy for bacteria (antibacterial), viruses (antiviral), fungi (antifungal) or protozoa (antiprotozoal). The term antibiotic, however, refers to antimicrobials produced by another living microorganism. Sulfa drugs and other synthetic antimicrobials are not classified as antibiotics, in the strictest sense of the word.

- Antibiotics may be as classified as either broad spectrum or narrow spectrum depending on how many types of microorganism are naturally susceptible to its action; and bactericidal or bacteriostatic depending on whether the antibiotic kills or inhibits the growth of the target bacteria. Antibiotics may also be classified according to their specific targets and modes of action in that they can be inhibitors of cell wall synthesis, cell membrane function, protein synthesis, nucleic acid synthesis or other metabolic processes.

- Antibiotics may be used therapeutically in animals for treating bacterial diseases, but they may also be utilized for non-therapeutic purposes such as growth promotion, prophylaxis and metaphylaxis.

- On a per-weight basis, large amounts of antibiotics are used for animal agriculture. It is a major public health responsibility of veterinarians to advocate the prudent and judicious use of antibiotics to preserve their future usefulness in treating both animals and people.

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