Review of Antibiotic Therapy in Non-lactating Cattle

Dan W. Upson, *DVM, PhD*
Emeritus Professor of Pharmacology
College of Veterinary Medicine
Kansas State University
Manhattan, Kansas 66506

The emphasis of this discussion will be the efficacy and safety of antimicrobial treatments in food producing animals as it relates also to the management of these animals. The objectives of the food animal industry are: A) produce a wholesome product, safe for human consumption; B) make a profit; C) meet the expectations of consumers and society as it; 1) meets their family budget for food, 2) nothing harmful is present, 3) the animal's welfare is regarded, 4) no adverse effects upon the environment, and 5) that the industry is a steward of the land.

Many centuries ago Asclepiades, a Greek physician who practiced in Rome, wrote about the philosophy of treatments, those philosophies are extremely important today in veterinary medicine. Asclepiades strongly advocated humane treatment and cure by restoring harmony. Humane treatment refers to reducing stress upon the patients and cure by restoring harmony simply means to correct any pathophysiological changes and restore the animal to normal health. In food producing animals this is extremely important because with these animals their ultimate performance is the bottom line. It must be remembered that efficacy is relative, not all treatments work 100%, but that safety cannot be compromised. The key decisions in food animal medicine are as follows: A) the decision to medicate; B) the regimen; C) decision of when to sell. If all of these three decisions are correct, the animal will benefit, the owner will benefit and society and the consumer will benefit.

To outline a summary of proper drug therapy one needs to consider all of the following: A) the choice of drug or drugs and we need to know what does the drug do, what are its actions, and what is the clinical response from these drugs; B) we also need to very carefully outline the objectives of the treatment regimen. This means we need to achieve the proper concentration of the drug at the proper site for the proper time. We also need to know where else does the drug go and what does that drug do when it goes there and how long does the drug stay there. When we consider that if you are treating an animal for pneumonia, we need the proper concentration of the antimicrobial in the lungs, we need it there quickly and we need it there long enough to take care of the bacterial infection. We also need to remember that the same cow has kidneys, liver, a central nervous system and we need to know if that drug goes there. If it does go there, what does it do there? For example, might it create a toxicity, and then in food producing animals we need to know how long it will stay there in order to take care of residue avoidance.

The therapeutic regimen is: 1) choice of drug or drugs; 2) the dose of the drug; 3) the route and method of administration; 4) how often will the drug be administered; and 5) how long will the drug be given to the animal. Everything revolves around the regimen. In order to set up a proper regimen that will achieve our therapeutic objectives and avoid any adverse reaction one must understand the kinetics of that drug and the dynamics of that particular drug. Ethics and jurisprudence also are a part of the consideration of a proper regimen. The economics of the treatment is also an important part of a therapeutic regimen. As Hippocrates stated "I will prescribe regimen for the good of my patients according to my ability and my judgement". **It is my judgement that improper dosage regimen of the proper drug is probably as common a cause of therapy failure or toxicity as the use of an improper drug.** Remember that Paracelsus admonished us that all substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy. The proper treatment regimen for successful recovery and no toxicity is the right drug at the proper site in the right amount for the right amount of time. Setting up a proper treatment regimen for a drug to achieve action and avoid toxicity or residue involves an understanding of the movements of the drug into, throughout, and out of the animal's body; plus the concentration of the drug over time in the animal's body, which is kinetics.

The metabolism of drugs is outlined in the summary schematic below (Fig.1). The plasma portion of blood is the central compartment for drug movement into, out of and around in the animal's body. With an intravenous injection, the drug is deposited, all of it,

into the blood. Drugs given by all other routes must be absorbed, thus the movement of drugs from the administration site into plasma is the absorption phase. Once the drug is in the central compartment or blood, it moves from there throughout the animal's body and this movement from plasma into the tissues is called distribution. As the animal's body gets rid of the drug this is called elimination. Drugs are eliminated principally by the kidneys into the urine and/or by the liver into the bile and into the feces. Drugs may be excreted in two forms: the free original drug which is in its active form; or a metabolite which is usually inactive.

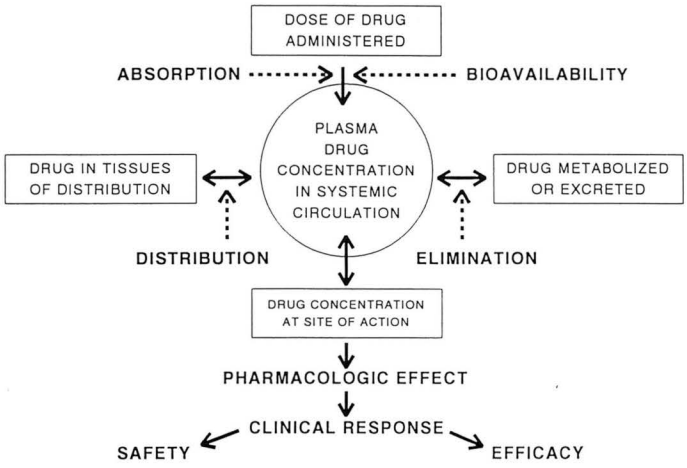

Figure 1.

Practical pharmacokinetics may simply be summarized as: A) Where does the drug go? B) How much of it goes there? (Concentrations). These concentrations are important in the plasma, and in the specific tissues. It is important to understand the relationship between plasma and tissue concentration. The how long or the rates refers to the time for the drug to get to a site and how long it will stay there. The time to reach the site of action may be estimated by peak plasma levels or the alpha half time of the plasma disappearance curve. The time of stay at a site in the animal's body is extremely important. The time at the site of action will determine efficacy and the time in the animal's body will give help in estimating the safe withdrawal times for food animals. The estimation of these times would be the beta half time of the plasma disappearance curve and/or tissue depletion times. Another way to look at pharmacokinetics is simply the concentrations of a drug in the animal's body over time or where and when does the drug appear and where and when does the drug disappear. In order to estimate some of these parameters, an important research tool is the plasma disappearance curve (Fig. 2). The plasma disappearance curve has two components, the first part of the curve will estimate how well does the drug distribute or penetrate from the plasma into the tissue. The steeper this curve the faster the drug leaves the blood and thus enters the tissue. The second component of this curve is the drug disappearing from the plasma because it is being eliminated. It is eliminated either by being biotransformed into an inactive metabolite and/or is being excreted. Another important parameter is the volume of distribution (Fig 3) which estimates the tendency of a drug to either stay in the plasma (drug with a low volume distribution) or readily leave the plasma and distribute to the tissues (drugs with a high volume of distribution). The volume of distribution depends upon physical and chemical characteristics of each drug.

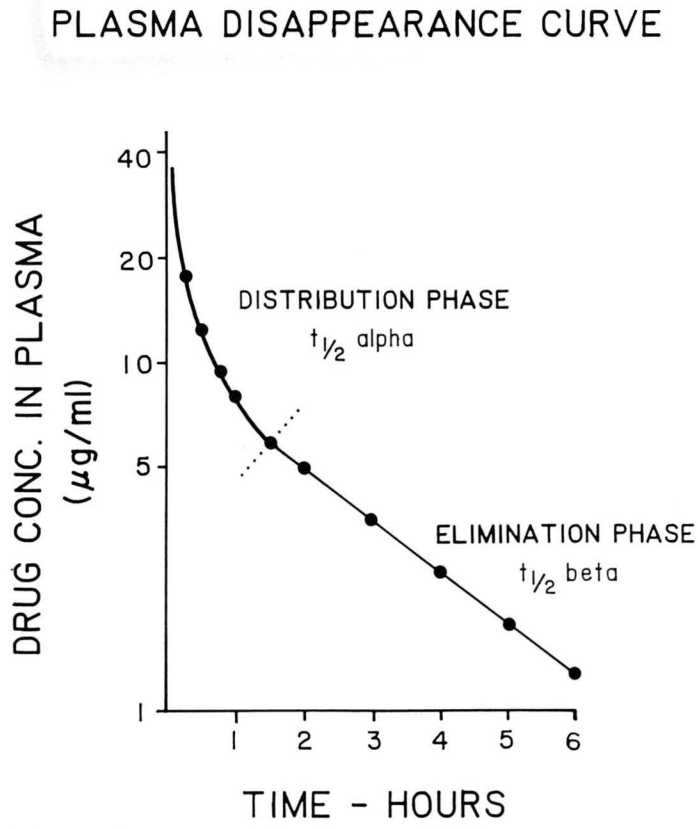

Figure 2.

Another important parameter is the area under the curve (AUC) which simply estimates drug concentration in plasma over time. If the drug is given intravenously, the area under the curve obviously must account for all of it. When a drug is given by any route other than intravenous the area under the curve quantitates the total amount of the drug that reaches the blood over time. In Figure 4 below, if a drug is given intramuscularly or subcutaneously or orally, blood concentrations will rise over time due to the absorption of the drugs in the blood. The peak quantity of drug in the blood is call the concentration maximum (C_{max}). The time at which the concentration max is reached is call the T_{max} or the time that this occurs. The declining slope of the blood concentration is the elimination phase of the drug. The T_{max} and C_{max} are extremely important as they

relate to blood levels of the drug in tissues where an infection might be.

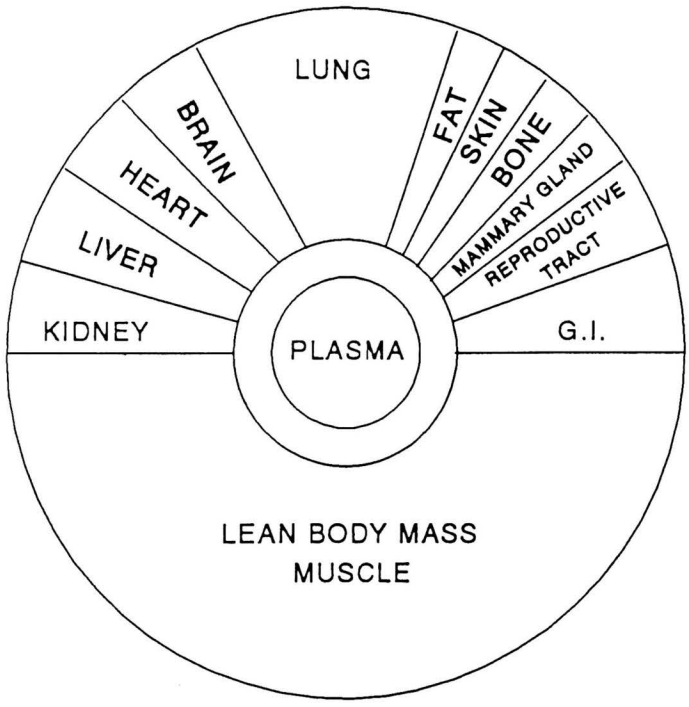

Figure 3.

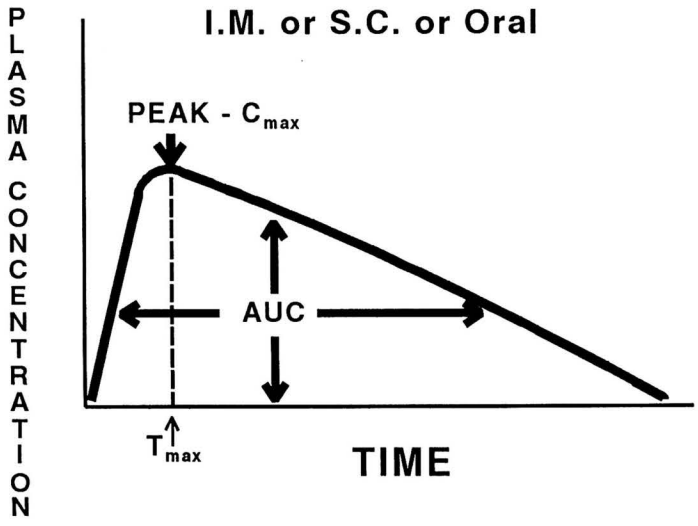

Figure 4.

In discussing cattle pharmacology, I think it is interesting to point out that under the general headings of cattle or bovines there are included in this list all of the following: A) baby calves, which are preruminant, B) Holstein calves which we know are different physiologically, C) there are calves on their mothers, but are now becoming mature ruminants, D) there are calves under the general heading of weaning calves or yearling calves that are weaned. The problem is that if we try to lump treatment by group we can make some serious regimen mistakes because these calves' weights could vary anywhere from 400 lbs. up to 800 lbs. Then there are the ranch origin calves and there are longhaul, highly stressed calves. There are mother cows which may be heifers or very old cows, they may be open or they may be pregnant, and again in setting up the treatments we do not dare lump these into treating by cow, we must treat by body weight because these cows could vary in weight anywhere from 700-800 lbs. up to 1800-2000 lbs. Then we must also include the fact that there are cattle whose origins go back to *Bos taurus* or *Bos indicus*.

The reticulo rumen is a magnificent organ, a great fermentation vat where the symbiotic relationship between the microflora of the rumen and reticulum furnishes the energy sources for the animal and the animal furnishes a proper environment for the microflora. This is a very dynamic physiological situation. I would like to point out that very large volumes of saliva are constantly secreted into the reticulo rumen, 10 to 12 liters per 100 lbs. body weight per day. This is a very large volume of saliva, it is very important as a buffer to the fermentation system which essentially produces end products which are acid. Have you ever wondered, when one treats a mature ruminant, if any of the drugs given get into the fluid of the reticulo rumen? It is obvious that if the drugs are given orally, then yes. Fairly high concentrations of the drug could be in the rumen fluid. It also appears that if there are high concentrations of drugs circulating in the blood supply to the wall of the rumen and reticulum that some of these drugs might down diffuse and enter the fluid. I think it is important also to remember that there is a physiological-pharmacological rule that states, for the most part any compounds found in blood will appear in saliva. If we assume this to be true, then blood with a high concentration of an antibiotic could be bathing the salivary glands, and there could be large concentrations of the drugs in the saliva, and remembering the amounts of saliva that enter the rumen and reticulum, it appears to me that this would be an avenue for considerable amounts of an antibiotic or sulfonamide to enter the fermentation vat. If this is true, then we need to know what the ultimate effect of an antimicrobial drug in the rumen fluid will be on the microflora and ultimately on the performance of the animal. We know that there are some antibiotics that, given at the appropriate time at low levels, can enhance performance. I would like to suggest that we also need to consider the fact that if an antimicrobial drug enters the rumen and because of its chemical characteristics would be trapped in rather high concentration in the rumen fluid, that it might have a very detrimental effect on the microflora and thus inhibit performance. It has been my observation in

discussing this problem with both producers and practicing veterinarians, that an example would be the drug Lincomycin. **It is my judgement that the poultry product LS-50 which is a combination of the Lincomycin and Spectinomycin should not be used in cattle.** There is evidence that Lincomycin could be trapped in the reticulo rumen and seriously inhibit the normal microflora. These animals might recover from the condition being treated and yet there will be a period of time when their performance just stands still and this is obviously economically very unsound. Personal discussion with a practicing veterinarian has also indicated that a group of stocker calves were mistakenly given feed contaminated with Lincomycin and there were losses of these calves and they did not eat properly and did not gain properly for several weeks.

Whether an animal is in health or in a state of disease is related to the imbalance between disease exposure versus body resistance, or harmful invaders versus body defenses. Proper drug selection relative to a successful treatment of bacterial disease is aimed at a complete recovery of the animal plus maximizing the animal's ability to continue at a high level of growth or production which equals performance. Proper treatment must be a partner with proper management, as Fig. 5 below illustrates. Proper function of the animal's body defense mechanism is a key to whether treatments will succeed or fail. For body defense mechanisms to function maximally, the animal must be properly nourished and be under a minimum of stress. The body defense mechanisms, whose job is to return the animal to a healthy status, are such things as the natural barriers, the skin and mucus membrane; respiratory mechanism such as a cough, sneeze and the cellular secretions and cilia combining in the respiratory "sweep", the inflammatory response to wall off an infected area, the immune response, and specialized cells such as neutrophils,

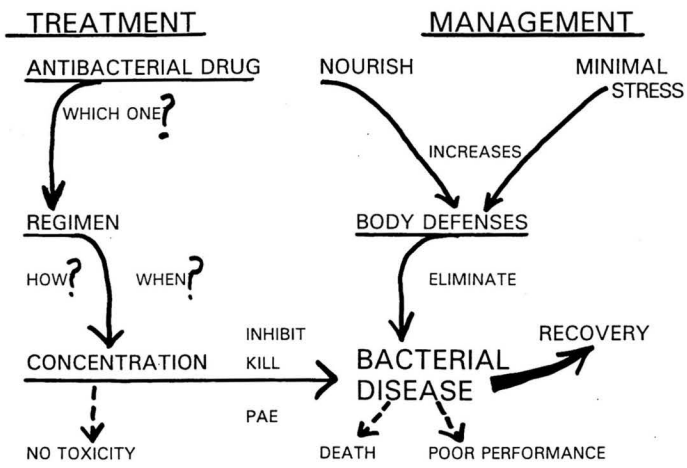

Figure 5.

macrophages and killer cells which phagocyitize and or destroy harmful viral bacterial invaders.

Just because pathogenic bacteria are present in an animal does not mean that there is disease. These bacteria must first invade the tissue or colonize. At this point, after the bacteria has invaded the tissues the harmful end results begin due to these bacteria that are toxins and toxins released by the damaged animal's cells. This is what produces disease. Now at the same time it is usual that these animals are not eating and drinking and this brings about metabolic changes which also can produce disease. Both of these together can produce a serious and even life threatening situation in the animal. To quote Dr. Steve Lewis, "sick cattle don't eat, cattle that don't eat get sick, and treated cattle that don't eat don't recover". The nourishment of the animal is extremely important because without energy and without the proper amino acids for building blocks the body's defense mechanism such as immunoglobulins and protective cells cannot be biosynthesized. This means that the ration must contain the energy sources and a high quality protein and that must ultimately be digested and absorbed to enhance the body's defense mechanisms. Limiting stress to these animals is extremely important. Stress is very detrimental to the proper function of the body's defenses if the harmful stresses continue. This stress releases hydrocortisone, and as we know hydrocortisone over a period of time is immunosuppressive. Hydrocortisone also affects the metabolism of the animal in that amino acids are broken down to form glucose. The animal is now in a state of catabolic metabolism and there is not an anabolic state necessary to bio-synethize new proteins such as the immunoglobulin.

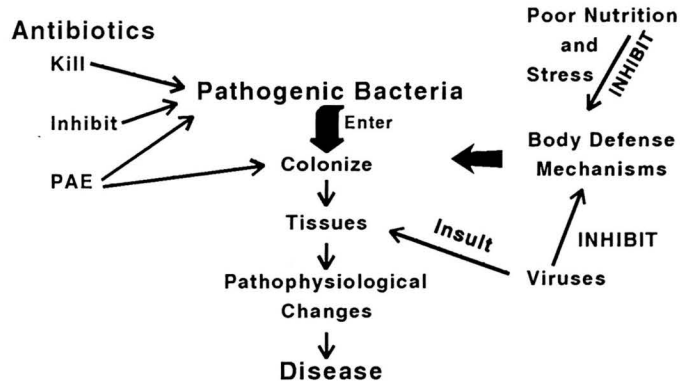

Figure 6.

A summary of the principles of antibacterial therapy might be as follows: A) detect, diagnose and treat the disease early. Treat with the proper antimicrobial or antimicrobials, the objective here is to aim the treatment. This means a specific antibacterial

against a specific disease. We must also consider the condition of the animal, the status of the homeostatic mechanisms and the body defenses.

What can antibacterial drugs actually do? What are the dynamics of these drugs? 1) They may kill the bacteria and thus are called bactericidal. 2) They may inhibit the multiplication of the bacteria and thus may be termed bacteriostatic. 3) They may also bring about what has been called the post-antibiotic effect, (PAE) a condition in which the bacteria are "crippled". All three of these dynamic actions are very much dependent upon the concentration of the drug and the organism involved. The classification of antibiotics as either bacteriostatic or bactericidal may be confusing. In order for a bacteriostatic categorized antibiotic to become bactericidal, one needs only to increase the concentration. So a bacteriostatic drug may be bactericidal if the concentration of the drug at the site of infection is high enough. The limiting factor here is, are these concentrations achievable, achievable in the tissues that are infected without bringing about toxicity. When tissue concentrations of an antibacterial drug are below the minimal inhibition concentration, the efficacy of that drug then depends upon: 1) The body's defense mechanisms; and 2) The post-antibiotic effect of the drug. What is the post-antibiotic effect? Antibacterial drugs have been shown to bring about a dilaterious effect on susceptible bacteria for a period of time after the concentration of the drug has fallen below the minimal inhibition concentration. What are the mechanisms or the end results of the post-antibiotic effect? I like to term the mechanisms as "the bacteria are crippled". 1) The bacteria have a decreased ability to grow and multiply. 2) the bacteria are more easily phagocytized. 3) The bacteria are more susceptible to the intercellular killing mechanism of leukocytes.

It is obvious that all of these will lead to a much better ability of the bodies' own defense mechanisms to do away with the infection. 4) There is an increased production of the bacterial autolytic enzymes, leading to their own destruction. 5) and very importantly in my judgement, the pathogenic bacteria have a decreased ability to adhere to and invade tissues within the body, they have a decreased ability to colonize. This simply says that there could be pathogenic bacteria in the animal's body at various tissue sites, but if the bacteria cannot colonize they have a reduced ability to produce disease. Whether or not the post-antibiotic occurs will vary with the different bacteria, their susceptibility, and the duration of the post-antibiotic effect varies with each organism and each drug. What is constant however, is that PAE is drug and concentration dependent, the greater the concentration, the greater the post-antibiotic effect duration. This simply means that drug regimens that achieve high tissue concentrations early and leave tissue levels below the minimal inhibition concentration for a period of time may be efficacious. To achieve these high tissue concentrations, the regimen would be either intravenous, or using an intramuscular injection of a very soluble drug form, for example a sodium salt of Penicillin G or ampicillin or amoxicillin. When these very soluble salt forms are given intramuscularly the C_{max} is very high and is reached in a very short period of time, a T_{max} of 15 to 20 minutes can be demonstrated. It needs to be considered that high peak concentrations in blood and thus tissues may be more important for efficacy than prolonged steady state concentration.The basic tenets of antimicrobial therapy simply stated would be as follows: 1) Remove the offending pathogens, 2) Correct any pathophysiology, 3) Restore to healthy physiological status the homeostatic situations in the animal, and 4) Avoid iatrogenic disease, which means caused by the treatment. What are the possible end results of iatrogenic disease? 1) Would be simple toxicity whether it be biochemical, cellular, organ or organ systems. 2) Injection site lesions, these injection site lesions are obviously important from the standpoint of being aesthetically unpleasing and must be trimmed out at the packing house. This can result in serious economic loss. Another situation that must be considered is that when an irritating product, whether the drug and/or its vehicle be the irritant, is injected, the body will react by initiating the inflammatory mechanisms. One of the end results of this inflammatory mechanism is that the body will attempt to wall off this irritating situation and this fibrinous capsule or wall that is put up around the injection site will slow the absorption of the drug from that site into the blood. This has two serious consequences, 1) Blood concentration and thus tissue concentrations will not be nearly as high, and efficacy is seriously impeded. The other is that as drugs are slowly absorbed, or "trickle in" to the blood over time, this can create serious need to extend the slaughter withdrawal time. If these slaughter withdrawal times are not extended, violative residues may be the end result. Another aspect we need to consider is that if a drug that is normally relatively tissue friendly is injected in too large a volume at any one injection site, this same walling off phenomenon may occur and result in low efficacy and the possibility of violative residues.

We have discussed the importance of a proper regimen of an antibacterial drug used in treating infectious disease as it relates to proper management of the animal for a complete recovery and a return to maximal performance. **It is my opinion that we must always remember that antibacterial drugs do not prevent or cure infectious disease.** They simply create an environment which allows the animal to cure itself. A summary that I have put together of the antibacterial therapy major problems is too little, too short, and too

late. Too little and too short simply means that the regimen was not proper, either there was too low a dose, the drug was not given frequently enough or the treatment was ended too soon. This is a very, very common cause of antimicrobial therapy failure. Too late simply means that the animals were not identified for treatment early enough. With too little and too short, what happens? It leaves a period of time when there is no or little antibacterial action. Treatment does not kill or remove all the pathogens and those that survive are the fittest bacteria. The remaining bacteria are tough and are resistent. The Darwin theory teaches this. Now these tough resistant pathogens can multiply rapidly and they form a new resistant population which obviously is harder to treat. When treatment is initiated too late the animal's body, defense mechanism are much less effective because they are "worn-out". What are the end results of the above problems? Poor treatment efficacy, an increased number of relapses, an increase in retreatments needed, increased dosages needed, increase treatment costs, longer recovery time, decreased performance of the animal after treatment, and an increase in chronic infection animals.

This discussion will concern the present therapeutic antimicrobials that are FDA, CVM approved for use in cattle. It will also include a brief summary of the kinetics and dynamics of these antimicrobial drugs by grouping.

1. Therapeutic Antimicrobials - Cattle

Present - FDA, CVM Approved.

1. The Penicillins. (Are Beta-lactams.)
   a. Procaine Penicillin G.
   b. Ampicillin Trihydrate.
   c. Amoxicillin Trihydrate.

Penicillins

1. Are primarily gram positive, some gram negative ability.
2. Have a low Vd, .2 to .4 L/KG.
3. Elimination is primarily renal, in free active form.
   Elimination half-time is 1 to 2 hours.

Penicillin G

		C_{max}	T_{max}
Sodium Penicillin G Potassium Penicillin G	I.M.	High	Fast
Procaine Penicillin G	I.M.	↓	↓
Benzathine Penicillin G	I.M.	Low	Slow

2. Cephalosporins. (Are Beta-Lactams.) Ceftiofur.

Cephalosporins

1. Spectrum - Depends upon their group. First Generation - Second Generation - Third Generation.

   Gram Positive → Gram Positive → Broad
   Increased Gram Neg.

   Ceftiofur - "Third Generation, Not Classic. Broad Spectrum.

Ceftiofur

2. Has a rather low Vd - .3 to .4 L/Kg.
3. Elimination is primarily renal.
   Some free active form.
   A metabolite, which is also active.
   The elimination half-time is 3 to 10 hours.

3. Tetracyclines.

Oxytetracycline.
a. Conventional. 50mg/ml and 100 mg/ml.
b. Long acting. 200 mg/ml.

1. Are broad spectrum.

   Bacteristatic → Bactericidal (↑ Conc.)

   Coccidia, Psittacosis, Anaplasmosis, Ehrlicia.
2. Vd is high, 1 to 2 L/Kg.
3. Elimination is both hepatic (free) and renal.
   Their elimination half-time is 10 to 15 hours.

4. Macrolides.

a. Erythromycin.
b. Tyolsin.
c. Tilmicosin.

1. Spectrum: Primarily gram positive and some gram negative.

   Bacteristatic → Bactericidal. (↑ Conc.)

2. Vd is 0.8 to 1 L/Kg.
3. Are eliminated both hepatic (60%) and renal.
   Their elimination half-time is 1 to 3 hours.

5. Aminoglycosides.

Neomycin - oral.

1. Spectrum is primarily gram negative. Are bactericidal.
2. Oral - are not absorbed to any extent.
3. Have a low Vd - .2 to .4 L/Kg. Have a high affinity for, and a high concentration in the kidney.
4. Elimination is renal, in the free form.

   Elimination half-time is 2 to 4 hours.
5. Are extremely nephrotoxic.
6. Because of 3, 4, and 5 above, 2 major problems may be brought about. They concentrate in, are toxic to the very organ that must excrete them which may seriously slow their elimination. This creates higher concentrations, which leads to serious toxicity and the likelihood of the drug appearing in the kidney for extended time, 8 to 18 months. **For the above reasons, plus a lack of safety and efficacy data in cattle, I support the position of the AVC, the AABP, NCA to use amino- glycosides in cattle only as labeled.**

6. Sulfonamides.

a. Sulfamethazine.
   Conventional - slow release.

b. Sulfadimethoxine.
   Conventional - slow release.

c. Sulfachlorpyridazine.
   (Calves under 1 month).

1. They are broad spectrum and are bacteristatic. Are cidal to coccidia.
2. Absorption.
   Oral

Well absorbed - T_{max}	6-8 hours
Intrauterine	Blood
Intramammary	Blood

3. Distribution.

   The Vd varies between the different sulfas from 0.3 L to 0.75 L/Kg.

   Lung concentration is approximately 50% of plasma concentration.

4. Elimination.

   Some hepatic biotransformation.

   Excretion is primarily renal, both free and metabolites.

   Elimination half-time is 1 to 12 hours. Extreme variation between sulfas.

7. These drugs are presently used in an extra label manner for the treatment of cattle.

1. Sodium Penicillin G (Human Label).
2. Potassium Penicillin G (Human Label).
3. Sulfachlorpyridazine (Baby Calf Label).
4. Sodium Ampicillin (Equine Label).
5. Spectinomycin (Poultry Label).
   Is an aminocyclitol.
6. Sulfadiazine plus Trimethoprim (Equine Label).

It would be a very useful tool if we had a crystalline salt form of one of the cillins with a cattle label.

8. These drugs, hopefully, will be available in the future. The following are seeking approval from FDA, CVM.

1. Spectinomycin.
2. Fluoroquinolones.
   a. Enrofloxacin.
   b. Danofloxacin.
   c. Saranfloxacin. (Has poultry approval)
      There may be others, that I am not aware of.
3. Florfenicol.

These antibiotics are badly needed in cattle practice in an effort to enhance efficacy of treatments. I also believe they would lead to decreased need for, and use of extra label treatments. This is a challenge for Dr. Sundloff and CVM.