# Systemic Antibacterial Drug Selection and Dosage

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The selection and use of antibiotics in clinical practice are dependent upon many factors, not the least of which are the particular drug use habits in the geographical area. Because most pathogens are susceptible to several antibiotics, successful therapy should not be unexpected with different drug use patterns. There are however, some important factors which should be given consideration when selecting antibacterial agents. Bacterial sensitivity is a prominent decision factor which is commonly of high priority. However, of nearly equal importance is the ability of the drug to achieve reasonable concentrations at the site of infection. Additionally the age and health of the animal should also be considered along with dosage preparations available, cost, toxicity, etc. It does no good to use a very potent oral antibiotic which does not penetrate to the site of infection or which is degraded by ruminal microflora before it can be absorbed. The lipid solubility and ionization at physiologic pH are important determinants of tissue pentration. Generally the more lipid soluble drugs which are little ionized at physiologic pH are most widely distributed in the body and are most likely to achieve reasonable concentrations in difficult-to-penetrate peripheral tissues such as brain and reproductive tract. The pH of the tissue is also important since tissues with a pH lower than blood (7.4) will trap basic antibiotics in them by causing increased ionization of the antibiotic. An example of this is the mammary gland with a pH of 6.8 to 7.0. In this case the basic aminoglycosides which are not lipid soluble will be found in higher levels in milk than some more lipid soluble drugs because they are trapped in milk and move from blood to milk more readily than milk to blood. Conversely acidic antibiotics may be found in lower than expected concentrations in tissues with a pH lower than blood. The tissue/serum ratios for a number of antibacterials are given in Table 1. As a general rule these relationships can be used to determine the need for dosage adjustment for infections involving specific tissues. In situations where an antibiotic is known to penetrate specific tissues poorly, the dosage may need to be increased appropriately.

Once antibiotic selection has been made, the primary concern should be to optimize dosage for maximal efficacy and minimal toxicity. Additionally, other factors such as economics, frequency of animal handling and route of administration will be important factors for both dosage determination and antibiotic selection. Often, because of cost or inadequate animal dosage information, the tendency is to use very low dosages which may be sufficient in some cases but in other cases may lead to the erroneous conclusion that the antibiotic is not effective. The dose may actually be appropriate but the dosage interval too long to sustain activity or vice versa with dose too low and the interval appropriate.

**An important principle to be emphasized is that there is no single optimal dose for any given antibiotic. There are too many variables such as host resistance, bacterial virulence, bacterial antibiotic sensitivity and site of infection to allow a single dosage recommendation to cover all situations. While many disease problems can be covered by routine dosage levels, special situations may require marked elevation of dosage or perhaps even allow reduced dosage.**

You have now selected an antibiotic for a specific case. What dose and dosage interval should you use? A desired serum or tissue concentration can be determined from the *in vitro* bacterial sensitivity data presented in Tables 2 and 3. The values presented are minimal inhibitory concentrations required to control growth of the organisms. In some instances 3 values are given, first the most sensitive organisms, second the majority of organisms, and third the more resistant group of organisms. It is generally desirable to select a dosage schedule which will provide serum or tissue levels equal to or exceeding the *in vitro* inhibitory concentrations for a substantial portion of the treatment

# TABLE 1
## Antibiotics for Systemic Use

| Antibiotic | Company | Oral Absorption | Lipid Solubility | Milk/Serum Ratio | Urine Levels | Remarks Drug Concentration in Tissues As a % of Serum Concentration |
|---|---|---|---|---|---|---|
| **Penicillins** | | | | | | |
| Pen G | numerous | low | low | 0.25 | high | |
| Dicloxicillin (Dicloxin) | Bristol | high | low | 0.25 | mod | 25% in lungs, 10% |
| Ampicillin | numerous | mod | low-mod | 0.25 | high | in bone |
| Amoxycillin | Beecham | high | low-mod | — | high | |
| Carbenicillin | (Beecham, Roerig) | low | low | — | high | — |
| **Cephalosporins** | | | | | | similar to penicillins |
| Cephaloridine (Keflodin) | Pitman-Moore | low | low | 0.25 | high | except cefazolin 30% |
| Cephalothin (Keflin) | (Lilly) | low | low | low | high | in bone |
| **Aminoglycosides** | | | | | | |
| Dihydrostreptomycin | numerous | low | low | 0.8 | high | |
| Neomycin | Upjohn | low | low | 0.5 | high | 25-30% in lungs |
| Kanamycin | Bristol | low | low | 0.7 | high | |
| Gentamicin | Schering | low | low | 0.4 | high | |
| **Spectinomycin** | Diamond, Upjohn, Abbott | low | low | 0.8 | high | similar to amino-glycosides |
| **Macrolides** | | | | | | broad distribution 500% |
| Erythromycin | Abbott, Diamond | variable | high | 4 | low | in lungs, reproductive |
| Tylosin | Elanco | high | high | 4 | low | tract, etc. |
| **Lincomycin** | Upjohn | mod | mod | 5 | low | broad distribution 40-50% + in lungs |
| **Tetracyclines** | | | | | | |
| Tetracycline | numerous | high | mod | 1 | low | mod. distribution, |
| Oxytetracycline | numerous | high | low | 0.8 | high | 50% + in lungs and |
| Chlortetracycline | Rachelle | high | mod | 0.9 | high | bone |
| Doxycycline | (Pfizer) | high | high | 1.5 | mod | broad distribution, 100% + |
| Minocycline | (Lederle, P-D)* | high | very high | 1.6 | low-mod | in lungs approx. 50% brain, bone prostate |
| **Chloramphenicol** | numerous | high | high | 1 | mod | broad distribution, 50% + in brain, 200% in lungs |
| **Trimethoprim** | B-W** | high | high | — | high | broad distribution to most tissues including brain, prostate, lung, etc. |
| **Sulfonamides** | numerous | | | | | |
| Sulfadiazine | | high | low | 0.15 | high | |
| Sulfadimethoxine | | high | mod | 0.25 | mod | |
| Sulfamerazine | | high | low-mod | 0.3 | high | broad distribution to most tissues but |
| Sulfamethazine | | high | mod | 0.3 | high | low in brain, prostate and other re- |
| Sulfamethoxypyridazine | | high | high | 0.3 | mod | productive tissues |
| Sulfathiazole | | high | low | 0.2 | high | |
| Sulfachlorpyridazine | | high | low | — | high | |

( ) Available only as human products.
*Parke-Davis.
**Burroughs Wellcome.

# TABLE 2

## In Vitro Bacterial Sensitivity, Micrograms/ml.

| Antibacterial | Bordatella bronchiseptica | Escherichia coli | Enterobacter aerogenes | Hemophilus spp. | Klebsiella aerobacter | Pasteurella | Pseudomonas aeruginosa | Salmonella typhimurium | Salmonella spp. | Mycoplasma agalactiae | Mycoplasma bovigenitalium | Leptospira pomona | Leptospira hyo | Leptospira icterohemorrhagica | L. canicola |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Penicillins** | | | | | | | | | | | | | | | |
| Penicillin G | — | 25 | 50 | — | 10/50/— | 0.4 / 2/100* | — | — | 10 | | | | | | |
| Oxacillin | — | — | — | — | | — | — | — | — | | | | | | |
| Ampicillin | 16 | —/ 5/40 | 100 | 5 | 50 | 0.5 / 2/100 | —/40+/— | 1/ 6/ 40 | — | | | | | | |
| Amoxycillin | — | 4 | 100 | 1 | 100 | 0.25/ —/— | — | 5 | 6 | | | | | | |
| Carbenicillin | — | 12 | 6 | — | 100 | — | — | — | 15 | | | | | | |
| **Cephalosporins** | | | | | | | | | | | | | | | |
| Cephaloridine | — | 5 | —/10/100 | 30 | 7 | 0.5 / 2/ 10 | — | 6 | 15 | | | | | | |
| Cephalothin | — | 6 | —/20/100 | — | 5 | 0.5 / 1/ 10 | — | — | 6 | | | | | | |
| **Aminoglycosides** | | | | | | | | | | | | | | | |
| Dihydrostreptomycin | — | — | 10 | 1-50 | 15 | 5 / 20/ 75 | — | 30 | — | 10+ | 50 | 0.03 | 0.03 | 0.06 | 6.5 |
| Neomycin | — | —/ 5/20 | 2 | — | 2 | 4 / 10/ 30 | — | 10 | 2 | — | — | 20 | 80 | 10 | 160 |
| Kanamycin | 32 | —/ 5/40 | 5 | — | 3 | 1 / 16/ 30 | —/ 40/ | —/ 5/ 40 | 2.5 | 10 | 50 | — | — | — | — |
| Gentamicin | 8 | 0.5/ 5/— | 2 | — | 2 | 2 / 6/ 12 | 1/ 5/— | —/ 5/— | 1 | — | — | — | — | — | — |
| **Spectinomycin** | —/100/— | 5 /15/40 | —/20/— | — | 5/20/100 | 10/ 40+ | —/40+/200 | —/30/100 | 20 | — | —/5/10 | — | — | — | — |
| **Macrolides** | | | | | | | | | | | | | | | |
| Erythromycin | — | 30 | 50 | — | 30 | 4 / 8/ 16 | — | 100 | — | 100 | 50 | 5.4 | 24 | 36 | 20 |
| Tylosin | — | — | — | — | — | 30 /100/— | — | — | — | 1 | 4 | — | — | — | — |
| **Lincomycin** | — | 40+ | — | — | — | —/ 20/— | — | — | — | 1 | —/1/ 5 | — | — | — | — |
| **Tetracyclines** | | | | | | | | | | | | | | | |
| Tetracycline | — | — | 2 | 0.3 | 4 | 0.4 / 5/ 25 | — | 10 | — | 1 | 8 | 1 | 1 | 10 | 8 |
| Oxytetracycline | 4 | 6 | 6 | 0.3 | 3 | 1 / 5/ 50 | — | 15 | — | 1 | 50 | 10 | 10 | 10 | 16 |
| Chlortetracycline | — | 6 | 6 | 0.3 | 6 | — | — | 40 | — | 50 | 5 | 1.6 | 0.3 | 2.4 | 4.8 |
| Doxycycline | — | 12 | 1.6 | — | 50 | — | — | — | — | — | — | — | — | — | — |
| Minocycline | — | 6 | 3 | — | 25 | — | — | — | — | — | — | — | — | — | — |
| **Chloramphenicol** | 16 | —/ 5/40 | 10 | 2 | — | 0.5 / 1/ 5 | — | —/ 5/ 40 | 5 | 5 | 5 | — | — | — | — |
| **Trimethoprim/Sulfadiazine** | — | 0.07/1.31 | — | — | — | 0.03/0.56 | — | — | 0.05/1 | — | — | — | — | — | — |

*First value are the most sensitive organisms, the second the majority of organisms and third the least sensitive group of organisms.

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+Divided about ½ and ½ between the two concentrations.

# TABLE 3

## In Vitro Bacterial Sensitivity, Micrograms/ml.

| Antibacterial | Corynebacterium pyogenes | Corynebacterium renale | Listeria monocytogenes | Nocardia asteroides | Staphylococcus aureus | Staphylococcus epidermis | Streptococcus spp. | Bacteriodes melaninogenicus | Fusobacterium nodosus | Fusobacterium necrophorum | Actinomyces bovis | Clostridium spp. | Clostridium tetani | Clostridium perfringens |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Penicillins** | | | | | | | | | | | | | | |
| Penicillin G | 0.1/ 0.5/ 1* | 0.2 | — | 100+ | 0.05/ 0.5/40 | 0.1 | 0.05 | 4-10 | 3 | 0.1 | — | 1 | — | — |
| Oxacillin | — | — | — | 25+ | 0.8 | 0.2/2 | 0.1 | — | — | 0.2 | — | — | — | — |
| Ampicillin | 0.1/ 0.5/ 1 | — | 0.3 | 25 | 0.1 / 0.7/10 | 0.2 | — | — | — | 0.1 | — | — | — | — |
| Amoxycillin | — | — | 0.1 | — | — | 0.2 | — | — | — | — | — | — | — | 0.05 |
| Carbenicillin | — | — | — | — | — | — | — | 4-10 | 3 | 0.2 | — | — | 25 | 25 |
| **Cephalosporins** | | | | | | | | | | | | | | |
| Cephaloridine | 0.1/ 0.5/ 2 | — | — | 25+ | 0.1 / 4 /— | —/0.1/— | —/ 0.1/3 | — | — | — | — | — | — | — |
| Cephalothin | 0.5/ 1/ 4 | — | — | 50+ | 0.2 / 1 /— | —/0.1/— | —/ 0.1/— | — | — | — | — | — | | 1 |
| **Aminoglycosides** | | | | | | | | | | | | | | |
| Dihydrostreptomycin | 1 /100/— | —/5/— | 10 | 10 | 2.5 | — | —/ 2 /50 | 500 | — | 200+ | 4 | 100 | 100 | 100 |
| Neomycin | 5 / 30/100 | — | 4 | — | 1.5 | — | — | 100 | — | 400 | — | 300 | — | 100 |
| Kanamycin | 8 / 25/ 60 | — | — | — | —/ 1 /— | — | — | — | — | — | — | — | — | — |
| Gentamicin | 2 / 5/ 15 | — | — | — | —/ 1 /— | — | — | 100 | — | 200 | — | — | — | 128 |
| **Spectinomycin** | — /100/— | — | 10 | — | —/40 /— | 30 | —/30 /— | 60 | —/30/100 | — | — | — | — | —/100/— |
| **Macrolides** | | | | | | | | | | | | | | |
| Erythromycin | .04/ 1/100 | .06/—/— | 0.2 | 25 | —/ 0.5/— | 0.5 | 0.5 | 1/ 5/— | —/10/100 | 25 | 0.3 | — | 1 | — |
| Tylosin | 0.1/ 50+ | — | — | — | 1 / 5 /— | — | 1 | — | — | | — | — | — | — |
| **Lincomycin** | — | — | — | 50 | —/ 0.1/— | — | 0.4 | 1 | 0.5 | 0.2/0.8 | — | —/2/10 | — | — |
| **Tetracyclines** | | | | | | | | | | | | | | |
| Tetracycline | — | — | — | 25 | 3 | — | — | 1/10/— | 1/ 2/— | 1 | — | 25 | — | — |
| Oxytetracycline | 2 / 50/100 | 8 | 9 | — | — | — | 1 | — | — | — | — | — | — | — |
| Chlortetracycline | 5 | 9 | — | — | 1 | — | — | — | — | — | — | — | — | — |
| Doxycycline | — | — | — | 10 | 1.6 | — | 0.4 | — | — | — | — | — | — | — |
| Minocycline | — | — | — | 8 | 0.8 | — | 0.4 | — | — | — | — | — | — | — |
| **Chloramphenicol** | 2 / 6/ 15 | 2 | — | 50 | / 5 /— | — | 2 | —/ 2/4 | 2 | —/3/6 | 5 | 10 | 2 | 5 |
| **Trimethoprim/Sulfadiazine** | — | — | — | — | 0.13/2.5 | — | 0.15/2.9 | — | — | — | — | — | — | — |

*First value are the most sensitive organisms, the second the majority of organisms and third the least sensitive group of organisms.

+Divided about ½ and ½ between the two concentrations.

period. It can be seen that for some bacteria low antibacterial concentrations may suffice if the more sensitive organisms are involved. Yet the next instance of disease encountered due to the same organism may be resistant to all but the highest doses of drug. Once a desired serum or tissue level has been decided, the dosage schedule may be determined. If the dosage schedule given in Table 4 fails to provide the appropriate serum level, adjustments can be made accordingly. In some cases an increase in dose will provide a proportional increase in serum concentration. This is true for IV preparations and for IM administration of some antibiotics such as aminoglycosides. These characteristics are given in the section on antibacterial groups. The serum concentrations given in Table 4 are maximal, midpoint in the dosage interval and at the end of the dosage interval. As such it can be seen that shortening the dosage interval may in some cases provide sufficient increase in serum concentration. Unfortunately the relationship between dosage and serum concentration is not readily predictable in some cases with oral or IM administration. This is particularly true for the slow absorption formulations such as procaine penicillin and trihydrate penicillins. In these cases increasing the dose will more effectively increase duration of action than serum concentration. Additionally administration of a drug by a route of slow absorption (SC) or by adding a second drug (procaine) to reduce absorption will also be accompanied by reduced serum levels. If the situation demands infrequent drug administration, dose must be increased. You don't get something for nothing. If you increase the dosage interval you must increase dose. In most cases this does not present a toxicity problem because toxicity is usually due to cumulative effects of the drug as with the aminoglycosides.

The foregoing comments are based on the ultimate goal of antibacterial therapy, attainment of adequate tissue levels to either kill the pathogen or control its growth. Adequate tissue levels are usually interpreted as levels equivalent to minimal inhibitory concentrations (MIC) of the drug (as determined *in vitro* or higher). The most readily available tissue for analysis and one which is in equilibrium with most other tissues is serum. Hence, serum levels of antibiotics are often used as an indication of adequacy of dosage. This relationship is not infallible, however, since other factors may also play important roles. The state of body defense mechanisms may significantly alter the efficacy of a given serum or tissue level. In some instances serum levels may not accurately reflect tissue levels, especially with antibiotics with high tissue levels, such as the macrolides. Since the ultimate test of antibiotic effectiveness is the response of the animal, the use of serum levels for predicting efficacy is only as valuable as its ability to predict the response of the whole animal. Generally this correlation has held, hence the use of serum levels for determination of antibiotic dosage. The fore-going limitations should, however, be kept in perspective while using such information clinically.

The situation with the sulfonamides is quite different than with many of the antibiotics. In this instance the correlation between attainment of *in vitro* inhibitory concentration requirements as *in vivo* serum concentrations and drug efficacy has not been as good as with most of the antibiotics. As a result in a general recommendation of 50 ug/ml (5mg/dl) serum has been widely accepted as the desirable serum concentration for all sulfonamides. Unfortunately little effort has been expended in veterinary medicine to determine MIC relationships between various bacteria and sulfonamides. Part of this deficiency may be attributable to marked effects of variations in culture media. Information abailable on human pathogens indicates considerable differences between sulfonamides as regards inhibitory concentrations *in vitro*. The relative potency varies with the pathogen but generally sulfachloropyridazine is the most potent of the commonly used sulfonamides. If these same types of relationships correlate with clinical efficacy, future work may allow serum concentrations and tissue/serum ratios to be useful in selection and dosage of sulfonamides as well as antibiotics.

### Pencillins

This group of antibiotics is bactericidal via inhibition of synthesis of cell wall materials necessary for maintenance of cellular integrity. The spectrum of action is quite broad for the group as a whole; however, specific individual penicillins may have a limited range of efficacy. Penicillin G is not only one of the oldest antibiotics, but remains one of the most useful. It is limited by its poor tissue distribution and its low sensitivity for gram negative bacteria. These limitations can often be overcome, however, by increasing the dosage since both cost and toxicity are low. Increasing the dose to increase tissue levels is best accomplished using either the Na or K salts IV or the Na salt IM. By these routes of administration, the increases in serum or tissue concentrations are nearly proportional to increases in dose. Dosage of procaine pencillin G must be increased markedly to produce a useful increase in serum or tissue level while benzathine pencillin G can only be used to provide prolonged low levels regardless of dose. The isoxazole pencillins such as oxacillin, cloxacillin and dicloxcillin are used primarily for infections involving pencillin G resistant (penicillinase +) *Staphylococcal spp.* They have the added advantage of being available for oral use.

The amphoteric pencillins such as ampicillin and amoxycillin have become popular because of their efficacy against many gram negative organisms. Although ampicillin is a very effective drug, its erratic oral absorption is an important limiting factor. With oral use, the dosage should be increased and administration accomplished several hours prior to or following feeding. Hetacillin is not appreciably better than ampicillin in the above respects. Amoxycillin, a very similar drug to ampicillin, does not share these restrictions as it is well absorbed in the presence of food. Na salt preparations of ampicillin are available for short

# TABLE 4
## Antibiotic Dosage and Serum Levels in Cattle

| Antibiotic | Dosage Formulation | Serum t½ Hours | Time of Max. Serum Conc. Hours | Dosage | | Serum Conc. ug/ml Maximum | Midpoint | Minimum |
|---|---|---|---|---|---|---|---|---|
| **Penicillins** | | | | | | | | |
| Penicillin G, Na | IM | 1.2 | 0.25 | 20,000 U/kg | 6hrs | 10 | 2 | 0.1 |
| Penicillin G, Procaine | IM/SC | — | 2 | 20,000 U/kg | 24hrs | 3 | 0.5 | 0.2 |
| Pencillin G, Benzathine | IM/SC | — | 6 | 20,000 U/kg | 3-4dys | 0.3 | 0.05 | 0.05 |
| Ampicillin, Na | IM/SC | 1.5 | 0.5 | 10 mg/kg | 6hrs | 14 | 1-2 | 0.3 |
| Ampicillin, trihyd | IM | | 2 | 20 mg/kg | 12hrs | 6 | 3 | 1 |
| Ampicillin, trihyd w/o milk | Oral 2-3 wk | | 2 | 20 mg/kg | 12hrs | 3 | 1.5 | 0.5 |
| Amoxycillin, trihyd | Oral calves | | 4 | 15 mg/kg | 12hrs | 5 | 3 | 0.5 |
| Amoxycillin, trihyd | IM | 1.5 | 2 | 15 mg/kg | 12hrs | 7 | 5 | 2 |
| **Cephalosporins** | | | | | | | | |
| Cephaloridine | IM | 0.6 | 0.5-1 | 10 mg/kg | 6hrs | — | 6 | 1 |
| Cephalothin | IM | — | 0.5-1 | 20 mg/kg | 6hrs | — | 1 | 0.1 |
| **Aminoglycosides** | | | | | | | | |
| Dihydrostreptomycin | IM | 2 | 1 | 10 mg/kg | 12hrs | 40 | 10 | 2 |
| Neomycin | IM | 2.5 | 1 | 10 mg/kg | 12hrs | 32 | 6 | 1 |
| Kanamycin | IM | 2 | 0.5-1 | 10 mg/kg | 8hrs | 30 | 12 | 3 |
| Gentamicin | IM | 2 | 0.5 | 3 mg/kg | 8hrs | 10 | 3 | 0.8 |
| **Spectinomycin** | IM | 1 | 1 | 25 mg/kg | 8hrs | 70 | 16 | 2 |
| **Macrolides** | | | | | | | | |
| Erythromycin | IM | 3-4 | 2 | 10 mg/kg | 24hrs | 1 | 1 | 0.5 |
| Tylosin | IM | 1.5 | 2 | 10 mg/kg | 12hrs | 0.8 | 0.7 | 0.4 |
| **Lincomycin** | IM | 3 | 1 | 10 mg/kg | 12hrs | 8 | 2 | — |
| **Tetracyclines** | | | | | | | | |
| Tetracycline | Oral | 13 | 2 | 10 mg/kg | 12 | — | 2 | — |
| Oxytetracycline | IV | 9 | — | 10 mg/kg | 12 | — | 4 | 2 |
| Oxytetracycline | IM | 11 | 4 | 10 mg/kg | 12/24 | 4 | 4/2.5 | 2.5/1 |
| Doxycycline | IV | 25 | — | 10 mg/kg | 24hrs | — | 2 | — |
| Minocycline | IV | 22 | — | 10 mg/kg | 24hrs | — | 2 | — |
| **Chloramphenicol** | IM | 3.5 | 4 | 40 mg/kg | 12hrs | 10 | 8 | 4 |
| **Chloramphenicol** | Oral, calves | — | 2-4 | 50 mg/kg | 12hrs | 5 | 4 | 1 |
| **Trimethoprim** | IV/IM | 1.5 | — | 25 mg/kg (as the combination product)* | 24hrs | — | — | — |
| **Sulfonamides** | | | | | | | | |
| Sulfachlorpyridazine | Oral | 1.2 | — | 30 mg/kg | 8hrs | — | — | — |
| Sulfadiazine | Oral | 2.5 | 8 | 150 mg/kg | 24hrs | 60 | 50 | 20 |
| Sulfadimethoxine | Oral | 12.5 | 12 | 110 mg/kg | 24hrs | 100 | — | 25 |
| Sulfamerazine | Oral | 7 | 12 | 150 mg/kg | 24hrs | 120 | 100 | 60 |
| Sulfamethazine | Oral | 6-9 | 12 | 150 mg/kg | 24hrs | — | 100 | 50 |
| Sulfanilamide | Oral | 6 | 8 | 150 mg/kg | 24hrs | 40 | — | 20 |
| Sulfapyridine | Oral | 6 | 12 | 150 mg/kg | 24hrs | 27 | — | 20 |
| Sulfathiazole | Oral | 1.5 | 8 | 150 mg/kg | 12hrs | 35 | 30 | 10 |
| Sulfabromethazine | Oral | — | 24 | 214 mg/kg | 72hrs | 100 | 80 | 20 |
| Spanbolets | Oral | — | 36 | 264 mg/kg | 96hrs | 110 | 90 | 33 |
| Sulfaethoxypyridazine | Oral | 11 | 12 | 55 mg/kg | 24hrs | 100 | 80 | 40 |
| Sulfaethoxypyridazine | Oral | 11 | 12 | 100 mg/kg | 48hrs | 125 | — | 36 |
| Sulfamethoxypyridazine | Oral | 8 | 9 | 100 mg/kg | 24hrs | 100 | 90 | 60 |

*Trimethoprim - sulfonamide combination.

duration, high serum levels while the trihydrate forms are analagous to procaine penicillin G in producing sustained low serum and tissue levels.

Additional pencillins are available with specific efficacy against *Pseudomonas spp.* These include carbenicillin and ticarcillin. Both are very effective but require high dosage (50 mg/kg). They can also be used concurrently with aminoglycosides but should be given separately. Carbenicillin is available as an IV/IM preparation and as an indanyl derivative for oral administration. Cost is a limiting factor in the use of these drugs.

**It should be pointed out that all of the penicillins are short acting drugs in the body; that is, they all have short duration of effect when given as the Na or K salt preparations. Half-lives of elimination in the 0.5 to 1 hour range are to be expected for all. This is in contrast to the procaine and trihydrate preparations, which are slowly absorbed and therefore have a much longer apparent sojourn in the body. These latter preparations also require much higher dosage to produce equivalent serum concentrations. Proportional increases in serum concentrations are obtainable only for the Na preparations. The penicillins (except for the amphoteric ampicillin, amoxycillin and carbenicillin) are acidic in nature and are more active in a slightly acidic medium where they are less ionized.**

### Cephalosporins

This is a little used group in veterinary medicine because of cost and other factors. They share many features with the penicillins including mechanism, spectrum of action, distribution and toxicity potential. This group may be of particular value in some cases for *Klebsiella spp.* infections. Some of the newer preparations such as cefazolin are useful against a broad specturm of gram negative bacteria. Again half-lives in the range of 1 hour or less are to be expected. Most of these are also acidic in nature.

### Aminoglycosides (aminocyclitols)

These antibiotics are widely used for gram negative bacterial infections, although dihydrostreptomycin, the prototype, has become much less effective in recent years. All are rapidly and well absorbed when given IM and poorly absorbed orally. The absorption is such that serum levels increase proportionately with dosage increases when given IM. Tissue distribution is limited although bronchiolar fluid levels reach approximately 25-30% of serum levels. Milk levels are also high reflecting the trapping of these basic drugs in the slightly acidic mammary gland. Distribution of these poorly lipid soluble drugs to the more inaccessible CNS and reporductive systems is very poor. Although these drugs may be trapped in an acidic environment they are more active at a slightly alkaline pH and may be considerably less active at pH between 6 and 7. The newer amikacin and tobramycin were developed primarily as anti-*Psuedomonas* drugs, although their spectra of action include many gram negative bacteria similar to kanamycin and gentamicin.

Spectinomycin is included in this group as an aminocyclitol and shares many common features except toxicity. It is of lower inherent antibacterial activity, but this can be overcome by increasing the dose since it is also of very low toxicity potential. It should be pointed out that spectinomycin is of very short duration in the body with a half-life on the order of 1 hour in most species. Like the aminoglycosides it is rapidly eliminated in the urine and has limited tissue dustribution. Spectinomycin is primarily bacteriostatic unlike the often bactericidal aminoglycosides.

### Macrolides

This is a group of highly lipid soluble bacteriostatic antibiotics which achieve excellent tissue pentration and relatively long tissue life. In such tissues as lung and mammary gland, drug concentrations may be 3 to 4 times serum levels. Similarly reproductive tract (prostate) levels are also high. A new experimental macrolide, rosamicin, is currently being developed as an antibacterial for prostatic infections in man. All of these basic drugs are more effective at a pH of 8 and much less at a pH of 7 or lower. Oral absorption is variable with erythromycin and may be reduced by feeding for some preparations. Absorption from IM injections is slow and because of the wide tissue distribution high serum levels are difficult to attain. Increasing dosage may be accompanied by a less than proportional increase in serum concentration. Most of these are effective on *Mycoplasma spp.*

### Lincomycins

Very similar as a group to the macrolides with good tissue distribution and reasonable oral absorption. Used mainly as antistaphylococcal antibiotics with particularly good penetration into bone. Drugs of this group are particularly effective against anaerobic pathogens (except *Clostridial spp.).* Lincomycin is also a basic drug with less ionization at a slightly basic pH.

### Tetracyclines

A mainstay in clinical practice against a broad array of pathogens although efficacy against some gram negative organisms has declined in recent years. The extensive tissue distribution of this group is of particular value with respiratory tissues. Although all the tetracyclines are well distributed to respiratory tissues including the sinuses, doxycycline appears to accumulate in bronchial fluids and may have particular value in chronic bronchiolar problems. Oral absorption is good in monogastrics, but questionable in ruminants. Although systemic effects are attainable by oral administration in ruminants, high serum levels are best

achieved by IV administration. In monogastrics, high oral dosage may be accompanied by high serum levels. Recently developed tetracyclines such as doxycycline and minocycline have much greater lipid solubility and penetrate the blood-brain and reproductive barriers to a greater extent. These are amphoteric drugs with ionization effects less predictable than with strictly acidic or basic drugs.

### Chloramphenicol

This potent bacteriostatic antibiotic remains one of the drugs of choice against many gram negative pathogens, although it is yet to be officially approved (FDA) for food animal use. It is also effective against many anaerobes. It is most effective when given IV or orally. Intramuscular use is accompanied by erratic absorption in many species (except ruminants). Oral administration in ruminants is not effective beyond 3 to 4 weeks of age because of ruminal degradation. The half-life of the drug in the body is somewhat variable between species, but is generally of short duration (except in the cat and perhaps the sheep and cow). In most species frequency of administration must be on the order of 3 to 4 times daily. The exception to this is the cat and sheep or cow, where 2 times daily may suffice. Chloramphenicol is well distributed, achieving serum concentrations or higher in many tissues. Concentrations in brain are somewhat lower, but still in the effective range. This is a neutral drug so ionization is not a consideration as regards efficacy.

### Trimethoprim

This bacteriostatic metabolic inhibitor which is available as a small animal oral preparation in combination with sulfadiazine (Tribrissen) has several very useful characteristics. It is very well distributed throughout the tissues of the body including the reproductive tissues and it acts synergistically with the sulfonamides such that very low concentrations are effective. The need for using only very low dosage greatly reduces the likelihood of toxic reactions. As of yet this combination has probably not attained the widespread acceptance which it merits. As a general rule, a dosage range of 20 to 30 mg/kg/day will be sufficient, but with more difficult problems, this may be given twice daily to offset the relatively short half-lives of these drugs in the body. The oral preparation is probably only effective in the preruminant calf, for others it must be given parenterally. Some restrictive tissues (reproductive) may limit penetration of the sulfonamide component with the resultant underdosing of the trimethoprim alone which may account for some therapeutic failures.

### Sulfonamides

This group of well recognized antibacterial drugs has long been used in veterinary medicine although in recent years their use has declined perhaps due to interest in antibiotics of more recent development. As a group, the sulfonamides have a broad spectrum of action and good tissue distribution throughout the body. The more lipid soluble forms (Table 1) achieve the best tisue levels, but all are generally low in the mammary gland due to their acidic properties. Since the half-lives of most of the sulfonamides are long and oral absorption slow, the daily dosage can usually be reduced to two-thirds or one-half of the initial dose. Of recent development are dosage forms with reduced absorption rates to prolong serum and tissue levels. **It should be pointed out that whenever reduced absorption occurs, dosage must be increased proportionately. You don't get something for nothing. If you have less drug absorbed initially it takes more to yield the same high tissue levels. In order to provide tissue levels for 3 to 4 days, more drug must be given.**

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