Systemic Antimicrobial Therapy in Beef Cattle: Pharmacologic and Therapeutic Considerations

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Factors which should be considered when selecting an antimicrobial agent for systemic treatment of a bacterial infection in beef cattle include:

1. Cost of an effective course of treatment.
2. The antimicrobial susceptibility of the causative bacterium.
3. The concentrations of the various candidate antimicrobial drugs which can be achieved in the precise location of the infection.
4. Rates of antimicrobial excretion and/or metabolism.
5. The shortest achievable treatment interval.
6. The location of the infectious process.
7. The pH in the area of infection.
8. The preferred route of drug administration.
9. Potential toxicologic problems which may result from adminstration of certain antimicrobial drugs.
10. The withdrawal period required prior to slaughter.

Each of these 10 factors will now be discussed in detail:

1. Cost:

Only a limited number of antimicrobial drugs are sufficiently inexpensive that their systemic use in commercial beef cattle can be economically justified. The sulfonamides (Table 1) and antibiotics (Table 2) which have been recommended[1] for systemic treatment of pasteurella infections in commercial beef cattle and their recommended dosages, routes of administration, treatment intervals and withdrawal periods are summarized. The use of other, more expensive antimicrobials may sometimes be justified in valuable individual animals and treatment regimens have been developed for some of them.[1]

2. The antimicrobial susceptibility of the causative bacterium:

Ideally, the causative bacterium should be isolated from the infectious process and the precise minimal inhibitory concentration (MIC) of each candidate drug determined *in vitro* using that specific isolate. In general, this is impractical in commercial beef cattle practice for several reasons:

(1). In life-threatening infections, treatment must be initiated before the results of laboratory testing will become available.
(2). MIC testing is unsuitable for sulfonamide drugs.
(3). MIC testing and Kirby-Bauer sensitivity testing are unsuitable for slow-growing and/or fastidious organisms like *Hemophilus somnus*.
(4). The cost of bacterial isolation and MIC testing prohibits its routine use in commercial beef cattle.

In practice, the experienced clinician begins by determining the nature and anatomic location of the bacterial infection. Through history-taking, physical examination(s), and sometimes necropsy examination(s), a tentative diagnosis (i.e., bronchopneumonia, footrot, peritonitis, etc.) is established. An antimicrobial drug is then selected for systemic treatment based on a knowledge of the kinds of bacteria which are most likely to cause that specific lesion/disease and their usual antimicrobial susceptibility patterns. For example, only three pathogenic bacterial species are commonly associated with fatal bronchopneumonia in feedlot cattle: *Pasteurella hemolytica, P. multocida* and *Corynebacterium pyogenes* (Table 3). The probability that sensitivity or resistance of these bacteria to the drugs listed in Tables 1 and 2 will be encountered is summarized (Tables 4-9). The MIC's of a number of antibiotics for these 3 bacterial species are presented (Figures 1-4).

3. The concentrations of the various candidate drugs which can be achieved in the precise location of the bacterial infection:

The concentrations of drug which are achieved in the plasma/serum of cattle, using various dosages and routes of administration, have been determined for a number of antimicrobials.[1] The concentrations of penicillin G, erythromycin and tylosin achieved with recommended dosages in urine of cattle have been determined (Figures 5-7). Much less is known about the concentrations of antimicrobial drugs which can be achieved in other biological fluids and secretions, especially in the diseased state. It would be useful to know the concentrations of various antimicrobial drugs that are achieved in intracellular fluid, interstitial fluid, peritoneal fluid, pleural fluid, pericardial fluid, cerebrospinal fluid, synovial fluid, aqueous humor, vitreous humor, bronchial secretions, milk, urine and abscess fluid of cattle. This knowledge would permit the clinician to avoid selecting a drug which does not reach effective (inhibitory) concentrations in the environment of the infecting bacterium.

It is generally belived that, in the presence of bacterial infection and inflammation, the concentration of almost *any* antimicrobial drug (Polymyxin B being an exception) in interstitial fluid and certain transcellular fluids (peritoneal fluid, pleural fluid, pericardial fluid, cerebrospinal fluid and

TABLE 1. Recommendations Concerning Dosages, Treatment Intervals and Withdrawal Periods for Sulfonamide Therapy in Cattle.

Sulfonamide	Dosage		Treatment Interval	Withdrawal for Slaughter (days)
	Priming	Maintenance		
Sulfamethazine, U.S.P.	1 1/2 Gr./lb.	3/4-1 Gr./lb.	24 hrs.	10
Sulfamerazine	1 1/2 Gr./lb.	1/2 Gr./lb.	12 hrs.	10
Sulfapyridine	1 Gr./lb.	1/2 Gr./lb.	12 hrs.	10
Sulfathiazole	1 1/2 Gr./lb.	1/2 Gr./lb.	6-8 hrs.	10
Vetisulid(R)	15-23 mg./lb.	15-23 mg./lb.	12 hrs.	5[a]-7[b]
Albon(R)[c]	25 mg./lb.	12.5 mg./lb.	24 hrs	5[a]-7[b]
Albon-S.R.(R)[c]	62.5 mg./lb.		4 days	21
S.E.Z.(R)	25 mg./lb.	25 mg./lb.	24 hrs.	16
S.E.Z.C-R(R)	100 mg./lb.		3 days	16
Sulfabrom(R)[d]	1½ Gr./lb.	1 1/2 Gr./lb.	48 hrs.	10
Spanbolet II(R)	1 bolus/150 lbs.		5 days	28
Hava-Span(R)[e]	1 bolus/200 lbs.		3 1/2 days	16
	1 bolus/100 lbs.		5 days	16

a After intravenous administration.
b After oral administration.
c Blood levels reported by the manufacturer with the recommended dose are only marginally therapeutic.
d Absorption from digestive tract not always reliable.
e Therapeutic blood concentrations not obtained during the 1st 14 to 18 hrs. after administration.

synovial fluid) will be equal to the free, unbound plasma/serum concentration.[2] The plasma concentrations achieved with the antimicrobials listed in Table 2 have been reported.[1]

When the pH of a biological fluid differs significantly from that of plasma, marked differences in the plasma: biological fluid drug concentration ratio may result, depending on the chemical nature of the drug. Due to the ion trapping phenomenon, antimicrobial agents which are organic acids (Table 10) tend to attain higher concentrations in biological fluids (such as bovine urine) which are more alkaline than plasma (pH 7.4) and lower concentrations in fluids more acid than plasma (such as milk).[3] The converse is true of organic bases (Tables 11 and 12). Weak acids give milk ultrafiltrate: plasma ultrafiltrate concentration ratios less than or equal to one; organic bases with the exception of aminoglycosides and spectinomycin (which are polar), attain concentration ratios greater than one.

4. *Rates of antimicrobial excretion and/or metabolism.*
5. *The shortest practical treatment interval.*

Factors 4 and 5 must be considered together. The most consistent and effective therapeutic results are achieved when it is possible to continuously maintain inhibitory antimicrobial concentrations in the bacterial environment throughout the course of therapy and until recovery has resulted. This is especially important when treating severe, life-threatening bacterial infections and when using bacteriostatic drugs.[3,4] In feedlot practice and range cattle practice, it is often impossible to administer treatment more frequently than once daily. Therefore, in this situation, it is generally desirable to select drugs (such as sulfamethazine, procaine penicillin G, oxytetracycline, and chloramphenicol) with which inhibitory plasma concentrations can be maintained with once-daily administration, rather than drugs (such as the aminoglycosides, macrolides, spectinomycin and some other sulfonamides) which are rapidly absorbed, excreted and/or metabolized and fall below inhibitory levels within 8 to 12 hours after administration.[1]

6. *The location of the infectious process:*

With most of the common, important bacterial diseases of the bovine, this is not an important consideration. In these diseases, the site of bacterial replication is primarily in the interstitial fluid, where antimicrobial drug concentrations (are presumed to) readily equilibrate with the free plasma drug concentration.[2] Consequently, it is not usually necessary to consider penetrative capacity when selecting an antimicrobial agent for use in beef cattle. However, there are certain infectious diseases/processes in which therapeutic results will be improved by the selection of an antimicrobial drug with high capacity to penetrate cellular membranes. These include:

(1). Intracellular bacterial infections, such as salmonellosis, listeriosis, corynebacterial infection, chlamydial infections and anaplasmosis (the latter a neorickettsial infection),

TABLE 2. Summary of Antibiotic Usage Recommendations.

Antibiotic	Proprietary name	Manufacturer	Packaging	Mode of action	Bacterial spectrum	Treatment interval	Dosage/ treatment	Route of administration	Withdrawal period-slaug. (days)
Oxtetracycline	Terramycin Injectable†	Pfizer	500 ml. vial 50 mg./ml.	Bacteriostatic	Broad Spectrum	24 hrs.	5 mg./lb. b.w.	s.c.	20[b]
	Liquamycin LA-200*	Pfizer	500 ml. vial 200 mg./ml.			48 hrs.	9 mg./lb. b.w.	i.m.	28[b]
Procaine Penicillin G†	Crysticillin	Squibb	100 ml. vial 300,000 units/ml.	Bactericidal	Mainly Gram +	24 hrs.	30,000 u./ lb. b.w.	i.m. s.c.	20[c]
Erythromycin†	Gallimycin Injectable	Abbott	200 ml. vial 200 mg./ml.	Bacteriostatic	Mainly Gram +	24 hrs.	20 mg./lb. b.w.	i.m.	30[c]
Dihydrostrepto-mycin**,†	Dihydrostreptomycin	Burns	100 ml. vial 500 mg./ml.	Bactericidal	Broad Spectrum	12 hrs.	25 mg./lb. b.w.	i.m.	120[c]
Tylosin**	Tylan 200	Elanco	250 ml. vial 200 mg./ml.	Bacteriostatic	Mainly Gram +	24 hrs.	20 mg./lb. b.w.	i.m.	20[c]
Chloramphenicol†	P/M Chloramphenicol, Oral Solution	Pitman-Moore	200 ml. vial 100 mg./ml.	Bacteriostatic	Broad Spectrum	12 hrs.	7.5 mg./lb.	s.c.	100[c]
	Chloramycetin Na Succinate	Parke Davis	1 Gm. vial			24 hrs. 12 hrs.	20 mg./lb. 15 mg./lb. b.w.	s.c. s.c. i.m.	
Neomycin †,[a]	Biosol Liquid	Upjohn	1 pint 140 mg./ml.	Bactericidal	Broad Spectrum	8 hrs.	40 mg./lb. b.w.	i.m. s.c.	120[c]
Ampicillin†	Polyflex	Bristol	10 gm. vial	Bactericidal	Broad Spectrum	12 hrs.	10 mg./lb. b.w.	s.c.	100[c]
Spectinomycin†	Spectinomycin Injectable	Diamond	30 ml. vial 100 mg./ml.	Bacteriostatic	Broad Spectrum	8 hrs.	15 mg./lb. b.w.	s.c.	100[c]

s.c. = subcutaneous, i.v. = intravenous, i.m. = intramuscular. *Approved by the FDA for use in beef cattle as indicated in the table. **Not recommended for treatment Pasteurella infections. †Dosage, treatment interval, and route of administration adjusted so as to assure an antibiotic concentration in the serum which is equal to or greater than the minimum inhibitory concentration for sensitive **P. hemolytica and P. multocida** isolates for no less than 67% of the period between treatments. [a] Approved only for oral and intramammary use. [b] Recommended by FDA. [c] Suggested by author.

TABLE 3. Results of Microbiological Examination of Lungs From 500 Fatal Cases of Bovine Bacterial Pneumonia.

Organisms isolated	No. of isolations	Frequency of isolation(%)
Mycoplasmas	331	86.2*
Pasteurella hemolytica	260	52.0
P. multocida	130	26.0
Escherichia coli (non-hemolytic)	70	14.0
Corynebacterium pyogenes	61	12.2
Proteus spp.	22	4.4
Pasteurella spp.	21	3.4
E. coli (hemolytic)	15	3.0
Negative (no growth)	13	2.6
Salmonella newport	10	2.0
Hemophilus somnus	7	1.4
Actinobacillus-like organisms	5	1.0
Streptococcus viridans	5	1.0
Alpha streptococci	4	0.8
Corynebacterium spp.	2	0.4
Enteric spp.	2	0.4
Enteric spp.	1	0.2
Alcaligenes fecalis	1	0.2
Flavobacterium spp.	1	0.2
Pseudomonas aeruginosa	1	0.2
S. dublin	1	0.2
S. typhimurium	1	0.2
Staphylococcus aureus	1	0.2
Streptococcus fecalis	1	0.2
Streptococcus fecium	1	0.2
All Pasteurellas	414	82.8

* A total of 381 lungs were examined for Mycoplasmas.

TABLE 4. Antimicrobial Agents To Which Pasteurellae Are Usually Sensitive:

Sulfonamides
Penicillin G
Ampicillin
Tetracyclines
Spectinomycin
Chloramphenicol
Neomycin

TABLE 5 Antimicrobial Agents To Which Pasteurellae Are Usually Resistant:

Dihydrostreptomycin
Erythromycin
Tylosin*

*Always resistant

TABLE 6 Antimicrobial Agents To Which **Corynebacterium pyogenes** Is Always Sensitive:

Penicillian G
Ampicillin

TABLE 7 Antimicrobial Agents To Which **Corynebacterium pyogenes** Is Usually Sensitive:

Chloramphenicol
Neomycin

TABLE 8. Antimicrobial Agents To Which **Corynebacterium pyogenes** is usually resistant:

Erythromycin
Tylosin
Tetracyclines
Dihydrostreptomycin

TABLE 9 Antimicrobial Agents To Which **Corynebacterium pyogenes** Is Always Resistant:

Sulfonamides
Polymyxin B

TABLE 10. Organic Acids:

Penicillins
Cephalosporins
Sulfonamides

TABLE 11. Milk to Plasma Drug Concentration Ratios:

Antimicrobials	R m/p
Penicillins	0.2-0.3[a, c]
Cephalosporins	0.25-0.3[a, c]
Sulfonamides	0.25-0.6[c]
Aminoglycosides	0.4-0.8[b, d]
Spectinomycin	0.6[b, d]
Tetracyclines	0.75-1.5[f]
Chloramphenicol	1.0[e, f]
Macrolides	3.5-7.0[d, f]
Lincomycin	4.5[d, f]

aIonized. bPolar. cOrganic acid (penetrative capacity underestimated). dOrganic base (penetrative capacity exaggerated). eNeutral. fLipid soluble.

TABLE 12. Organic Bases

Aminoglycosides
Spectinomycin
Macrolides
Lincomycin
Trimethoprim

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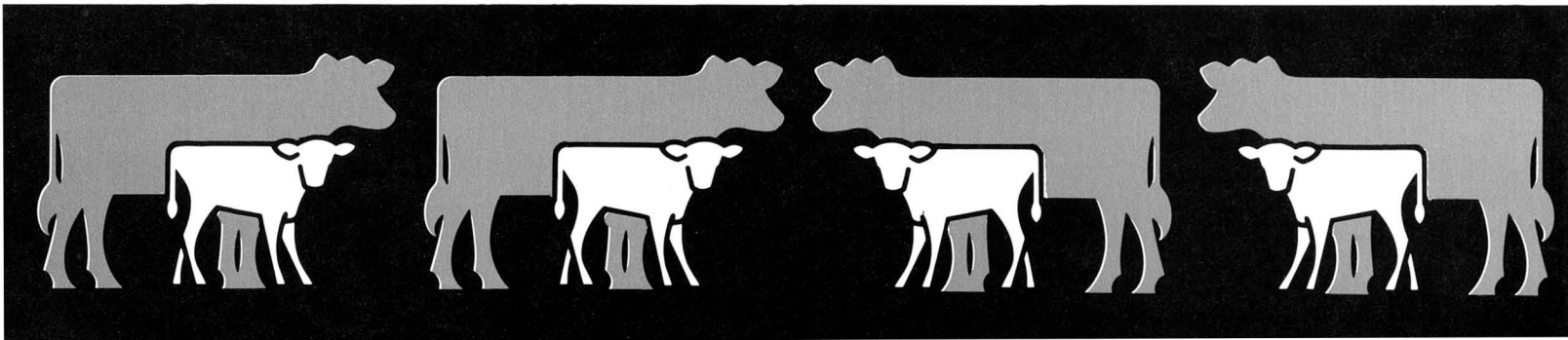


(2). abscesses[5], and

(3). infections of the interior part of the eye (uveitis, panophthalmitis).

There is also a theoretical advantage for cell membrane-penetrative and antimicrobial drugs in the treatment of bacterial serositis (synovitis, pleuritis, peritonitis, and or pericarditis), meningioencephalitis and mastitis. It is presumed that plasma concentrations of any antimicrobial drug will rapidly equilibrate with those in serous and synovial fluids, cerebrospinal fluid and mastitic milk when bacterial infection and inflammation are present. However, as the infection is controlled and inflammation subsides, the concentrations of less-penetrative drugs may sometimes fall below effective levels in these locations, before the bacteria are completely eliminated. Consequently, relapse or recurrence may sometimes result.

Factors which influence the movement of antimicrobials across cell membranes are:

(1). The extent of plasma protein binding:

A drug must be able to leave the plasma in order to reach the sites of the most common bovine bacterial infections. Few, if any, infections are limited to the intravascular space. Nearly all antimicrobial drugs are, to some degree, bound to plasma proteins and especially to albumin. In general, plasma protein binding is seldom a factor in the effectiveness of antimicrobial drugs, except when it exceeds 80%.[3] Sulfadimethoxine is one of the few antimicrobials commonly used in cattle in which plasma protein binding approaches this critical value (Table 13).

(2). The degree of ionization or polarity:

The capacity of antimicrobials to penetrate cellular membranes varies inversely with their degree of ionization or polarity (Tables 11 and 13). Some of the more highly ionized or polar antimicrobials are shown (Table 14).

(3). The degree of lipid solubility:

The capacity of antimicrobials to penetrate cellular membranes is enhanced by the characteristic of lipid solubility. Some lipophilic antimicrobial agents are shown (Table 15).

(4). The nature of the compound (organic acid or organic base).

This has been previously discussed.

When a bacterial infection is localized within the urinary tract (urethritis, cystitis, pyelonephritis), it is essential to select an antimicrobial agent which is excreted in the urine in the active (non-metabolized) form and in high concentrations. Fortunately, this is a characteristic of nearly all antimicrobials which are likely to be used in the bovine. The elimination processes of these drugs are summarized (Tables 16-19). Chloramphenicol is eliminated entirely by hepatic metabolism in most species. However, substantial concentrations of active chloramphenicol are present in urine of cattle treated with dosages recommended for pasteurella infections.[6]

TABLE 13. Comparison of the Pharmacokinetics of Sulfonamides in Cattle [3]

Compound	% non-ionized in plasma (pH 7.4)	Protein binding (%)	Volume of distribution (l/kg)
Sulfanilamide	100	<20	1.08
Sulfadiazine	9	14	0.75
Sulfamethazine	50	70	0.44
Sulfadoxine	4.8	48-66	0.37
Sulfadimethoxine	3.8	80-85	0.31
Sulfamethoxazole	3.8	62	0.30

TABLE 14. Ionized/Polar Antimicrobial Agents.

Penicillins*
Penicillin G
Ampicillin
Aminoglycosides**
Dihydrostreptomycin
Neomycin
Kanamycin
Gentamicin
Cephalosporins*
Aminocyclitol**
Spectinomycin

*Ionized. **Polar.

TABLE 15 Lipophilic Antimicrobial Agents

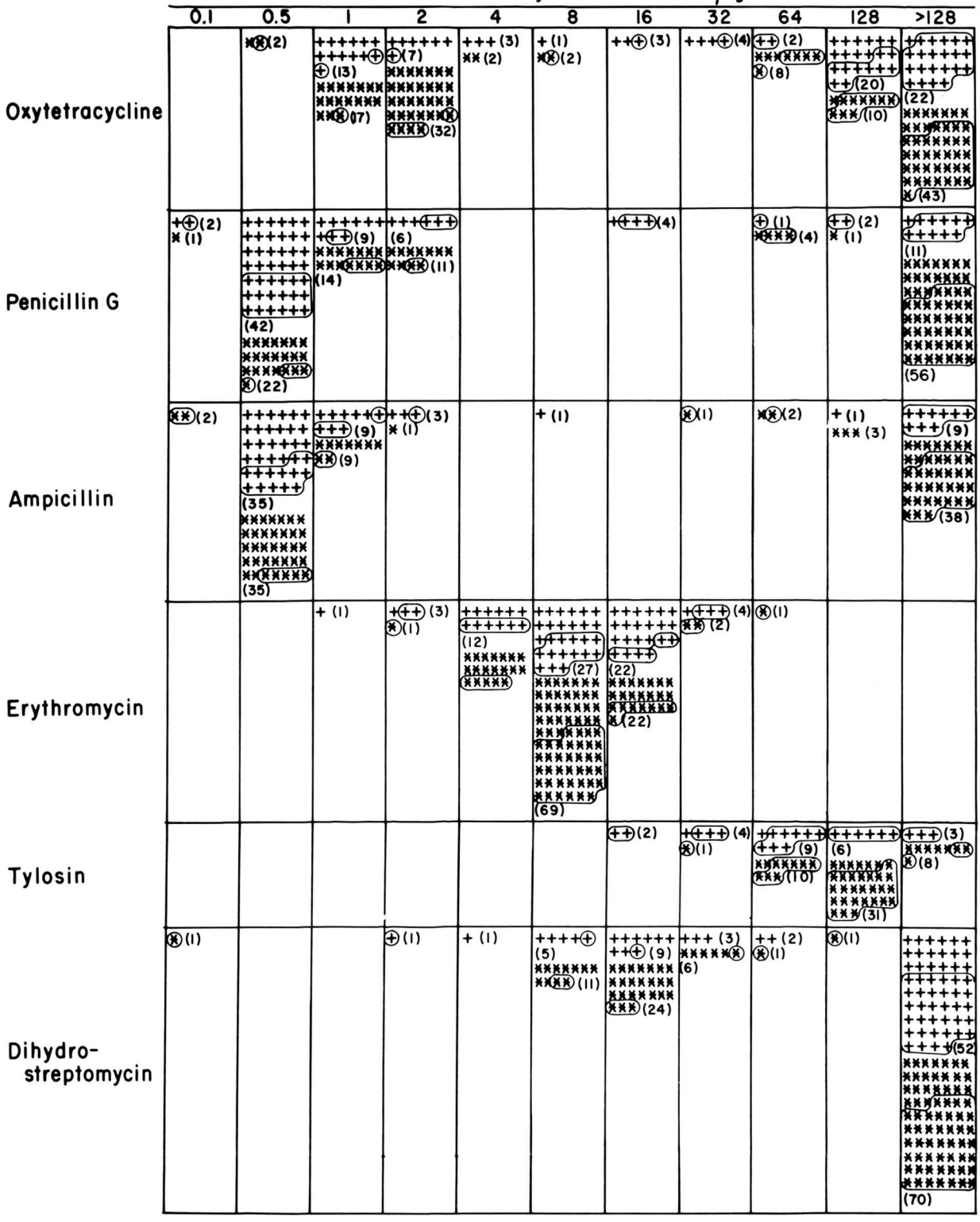
Sulfonamides*
Tetracyclines
Macrolides
Erythromycin
Tylosin
Spiramycin
Oleandomycin
Carbamycin
Chloramphenicol
Lincomycin
Trimethoprim

*Less so than the others listed.

TABLE 16. Antimicrobials Eliminated Entirely by Renal Excretion.

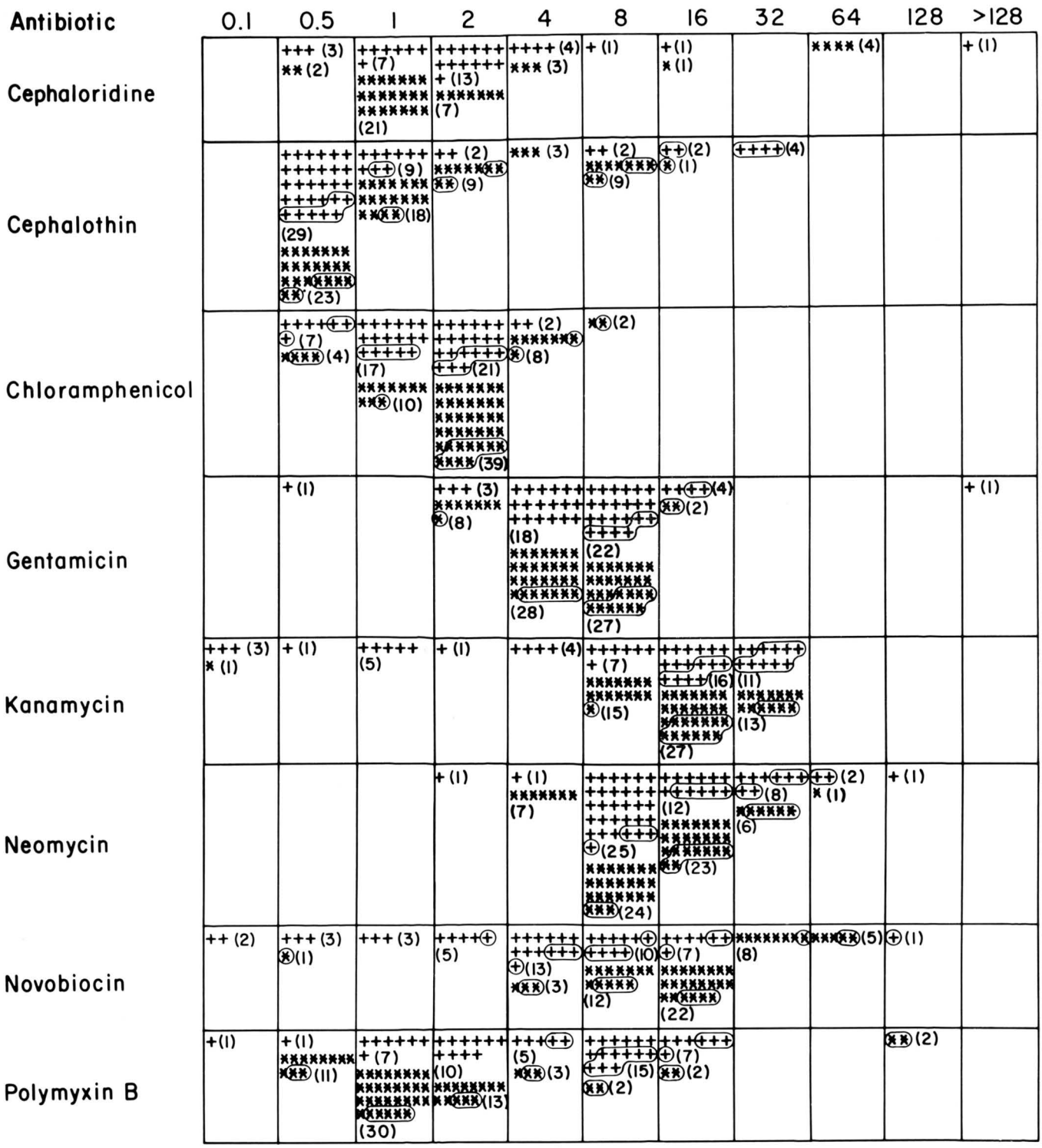
Penicillins
Cephalosporins
Aminoglycosides
Spectinomycin
Polymyxin B

Minimum Inhibitory Antibiotic Concentrations for *Pasteurella hemolytica* and *Pasteurella multocida*



+ A *P. multocida* isolate from nasal secretions of a sick bovine
⊕ A *P. multocida* isolate from a pneumonic bovine lung
✱ A *P. hemolytica* isolate from nasal secretions of a sick bovine
⊛ A *P. hemolytica* isolate from a pneumonic bovine lung

Minimum Inhibitory Antibiotic Concentrations for Pasteurella hemolytica and Pasteurella multocida



+ A single P. multocida isolate from nasal secretions

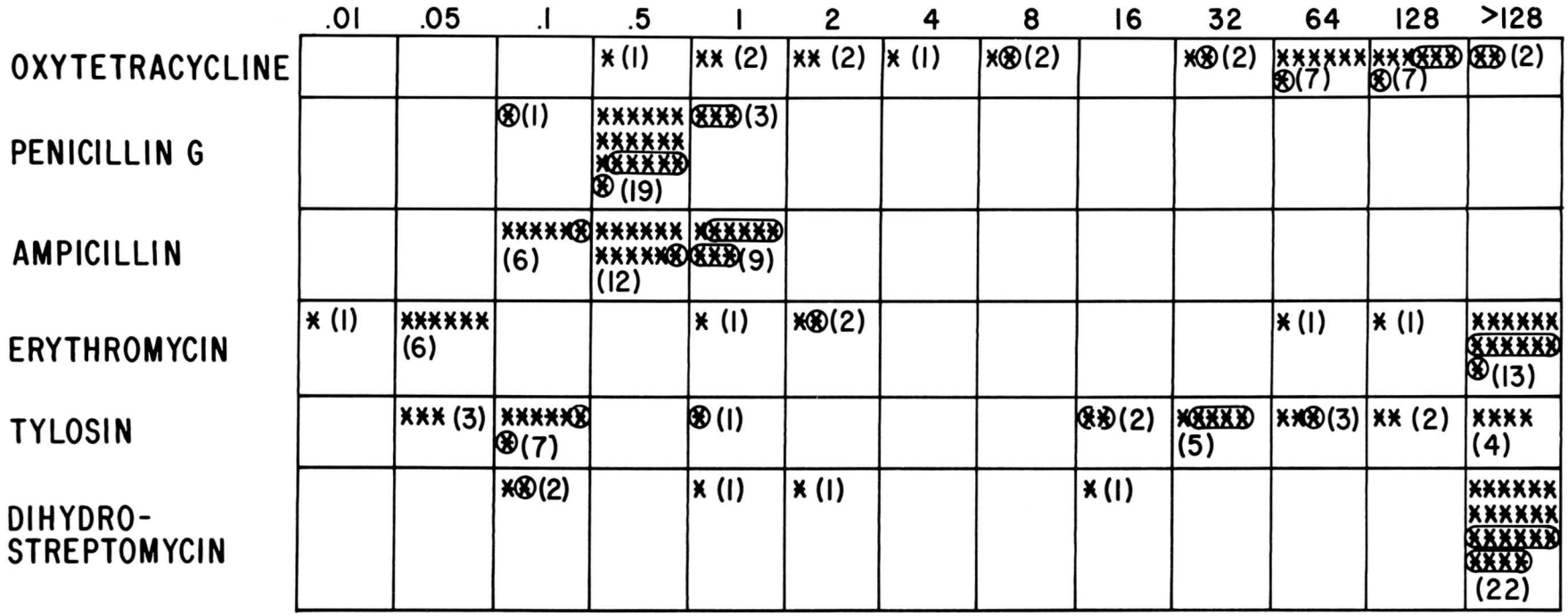
⊕ A single P. multocida isolate from pneumonic lung

* A single P. hemolytica isolate from nasal secretions

⊗ A sinale P. hemolytica isolate from pneumonic lung

MINIMUM INHIBITORY ANTIBIOTIC CONCENTRATIONS FOR CORYNEBACTERIUM PYOGENES

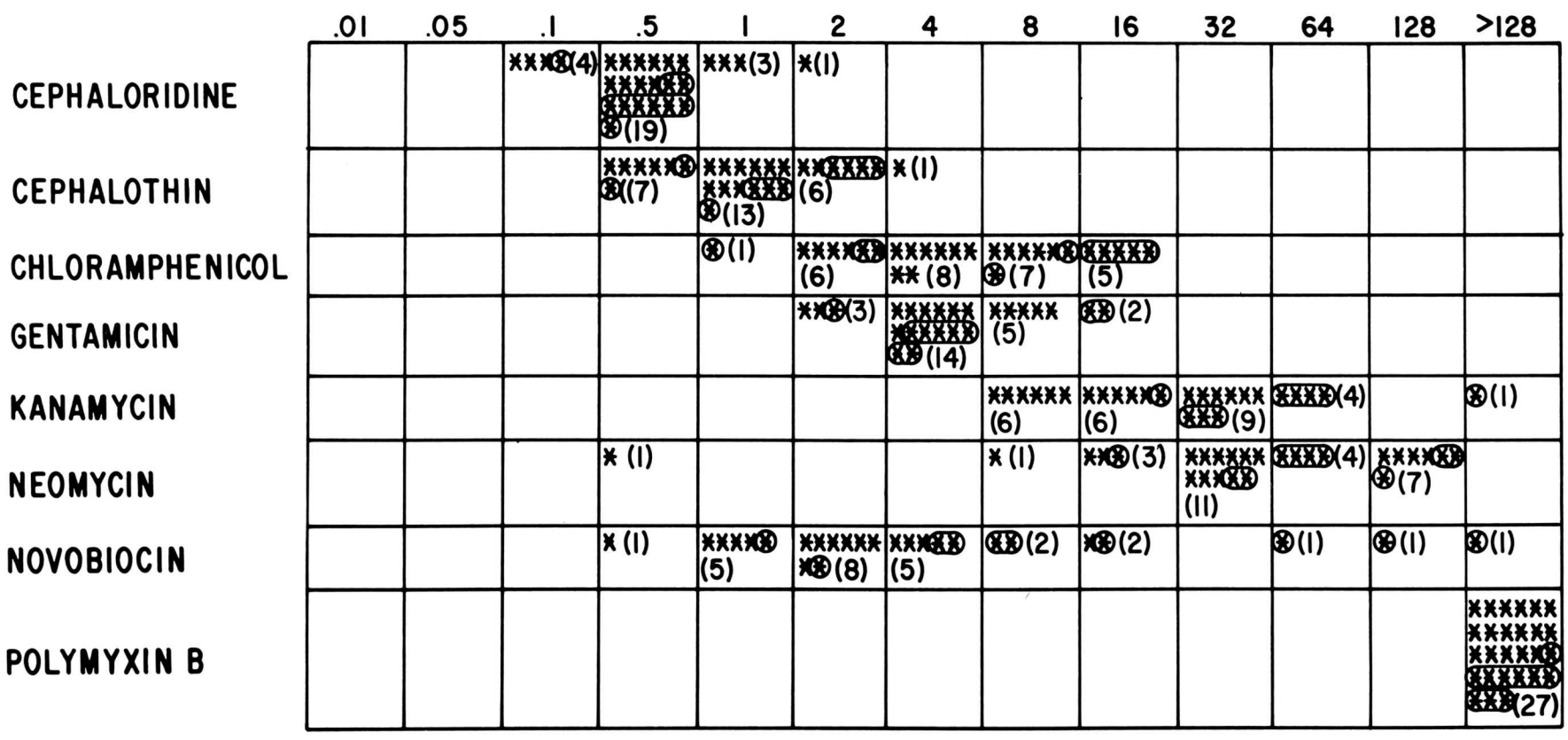
Minimum Inhibitory Concentration (µg/ml)



* A single isolate of C. pyogenes from a non-pulmonic infectious process.

⊗ A single isolate of C. pyogenes from a pneumonic lung

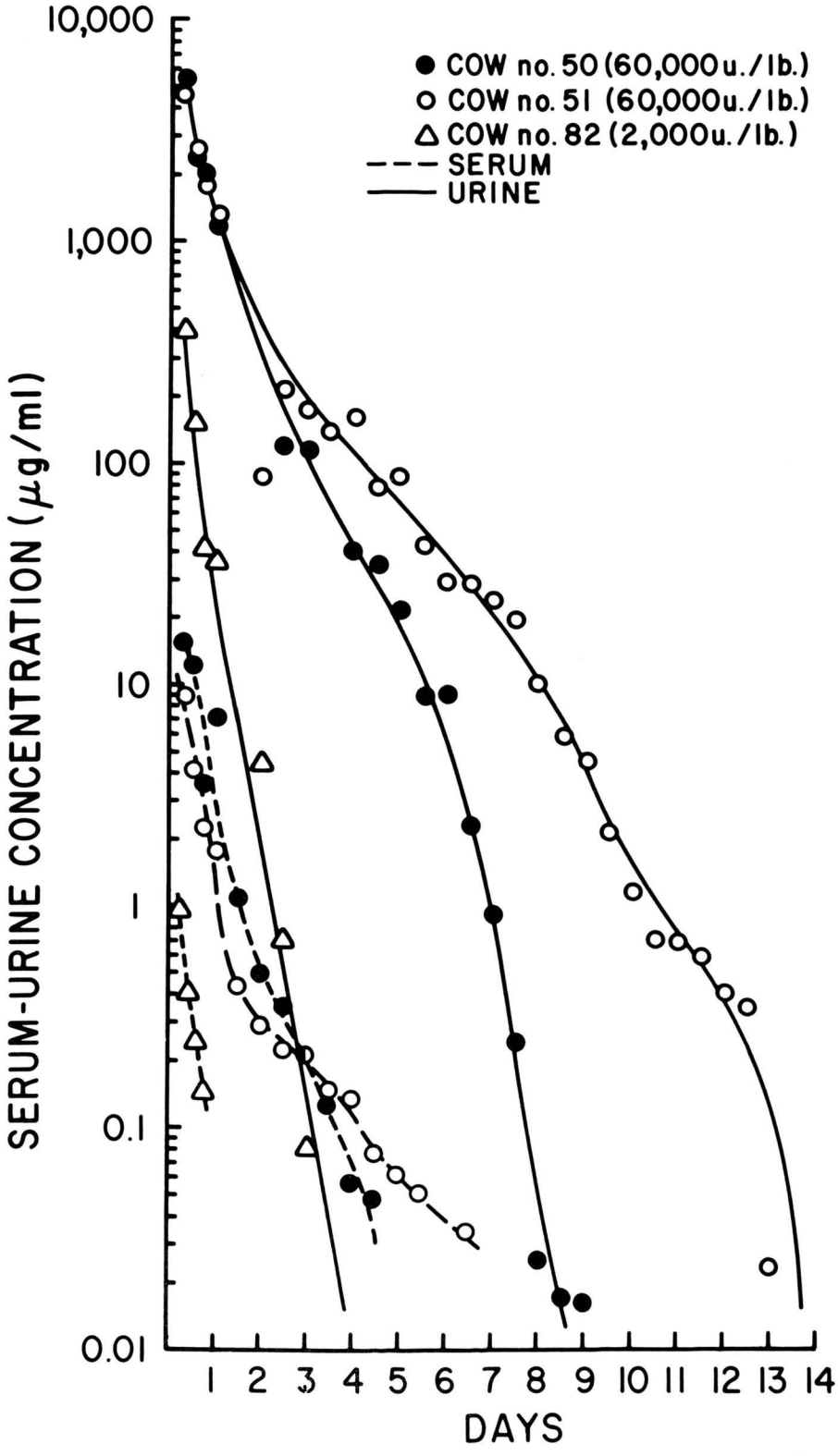
MINIMUM INHIBITORY ANTIBIOTIC CONCENTRATIONS FOR CORYNEBACTERIUM PYOGENES



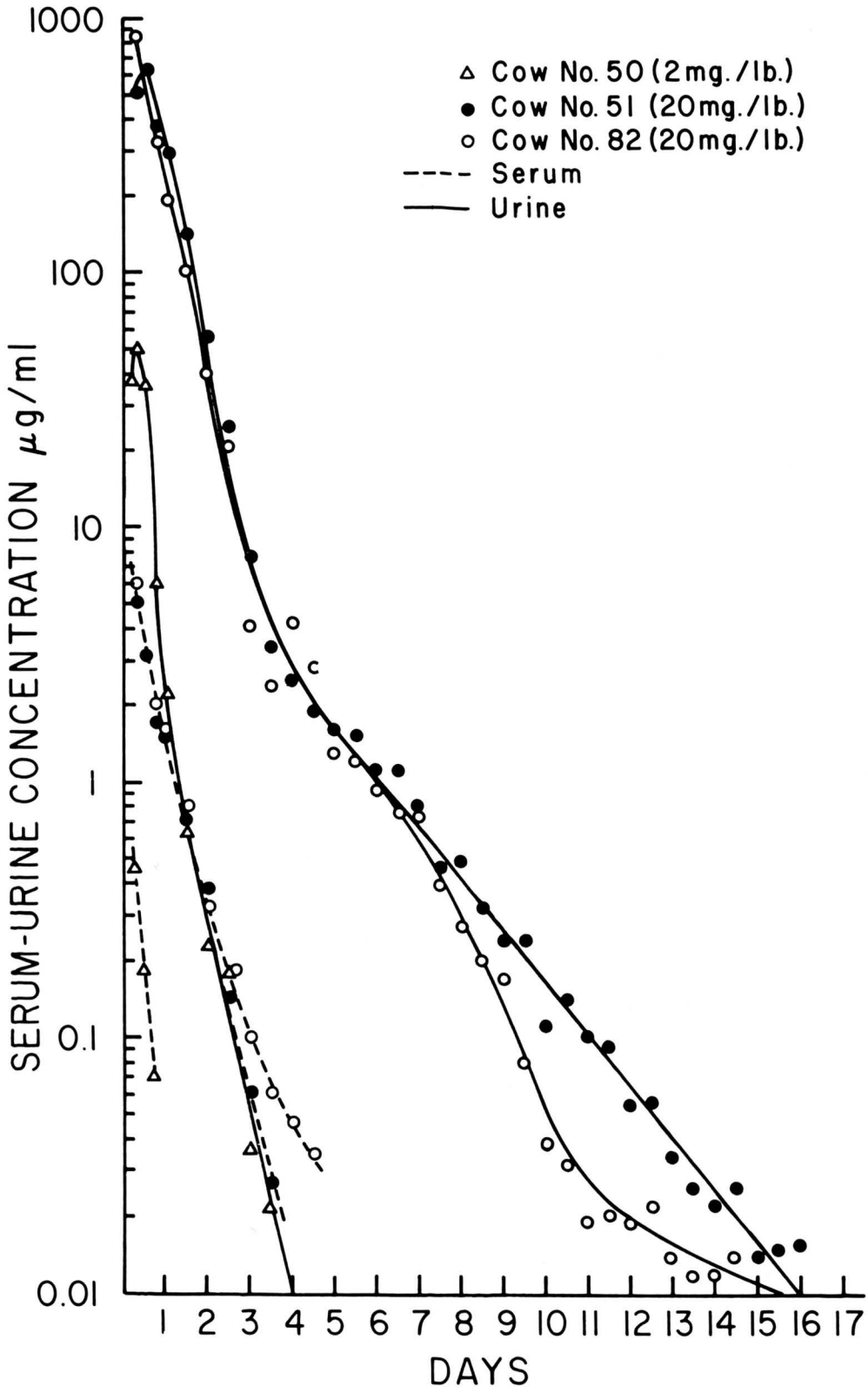
* A single isolate of C. pyogenes from a non-pulmonic infectious process.

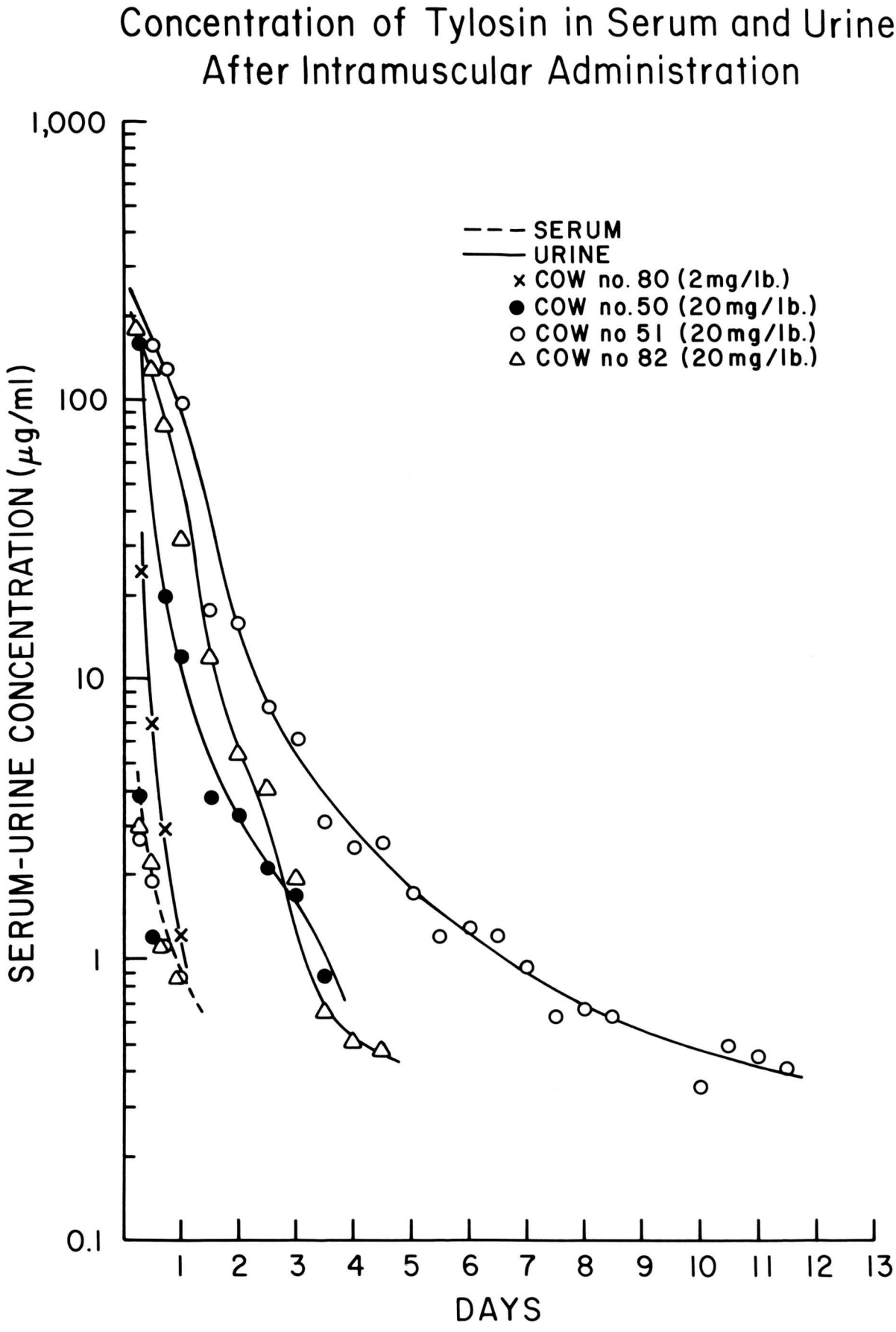
⊛ A single isolate of C. pyogenes from a pneumonic lung.

Concentration of Penicillin G in Serum and Urine After Subcutaneous Administration of Procaine Penicillin G, Aqueous Suspension



Concentration of Erythromycin in Serum and Urine After Intramuscular Administration





Since most of these drugs are eliminated by renal excretion, sufficiently high urinary concentrations are achieved that most species of pathogenic bacteria (even many of those classified as antimicrobial-resistant by the Kirby-Bauer method of sensitivity testing) will be inhibited (Figures 1 and 5-7). Even urinary tract infections with some penicillin-resistant strains of bacterial species like *E. coli* can be effectively treated using systemic penicillin G therapy.[7] When interstitial nephritis is present, however, inhibitory drug concentrations must be achieved in the interstitial fluid of the kidney as well as in the urine. Consequently, the use of a drug to which the infecting bacterium is classified as sensitive (by Kirby-Bauer testing) is necessitated.

7. The pH of the infectious process:

The pH of fluid within abscesses and areas of tissue necrosis is often highly acidic in reaction.[5] The activity of some antimicrobial agents is substantially reduced or abolished in this environment (Table 20). Antimicrobial drugs which are less adversely affected by acid pH include oxytetracycline (which is most active at pH 5.5), chloramphenicol, sulfonamides and the broad spectrum penicillins such as amoxycillin and, to a lesser extent, ampicillin. The utility of tetracyclines and sulfonamides for treatment of abscesses in cattle is compromised by the fact that the most common causative bacterium (*C. pyogenes*) is usually resistant to these drugs (Table 8 and Figure 3). In addition, sulfonamides are not very active in the presence of pus, because of its nucleic acid content.[5].

8. The preferred route of administration:

This is not ordinarily a major consideration. Some veterinarians prefer to dispense oral medications to clients for follow-up treatments. This limits one's choice to a sulfonamide, except in young calves. Pre-ruminant, milk-fed calves can be orally medicated with a sulfonamide, chloramphenicol, a trimethoprim-sulfonamide combination preparation, ampicillin or erythromycin. Tetracyclines are poorly absorbed from the ruminant stomach[1] as well as from the stomach of milk-fed calves. Therapeutic oral administration of other antibiotics, such as erythromycin, or ampicillin, to the functional ruminant is likely to result in adverse effect on ruminal flora.[3]

9. Potential toxicologic problems:

Antimicrobial toxicoses are not a frequent occurrence in cattle. Anaphlactic-type drug reactions are, perhaps, the most common problem encountered. These are seen most frequently within 30 minutes of parenteral administration of procaine penicillin G or certain oxytetracycline formulations. Affected cattle rapidly become prostrate and often die. Intravenous administration of 5 ml of epinephrine, U.S.P. 1:1000, can often be curative. This comparatively rare event cannot be anticipated or avoided and is not a consideration in selecting an antimicrobial drug.

Nephrotoxicosis, ototoxicosis and neuromuscular blockade may sometimes result from use of certain antimricrobials, especially aminoglycosides.

Nephrotoxicosis is the most important of these toxic syndromes in cattle practice. Causative antimicrobials are listed (Table 21). Neomycin nephrotoxicosis is being seen with increasing frequency in calves treated for non-responsive (presumably antimicrobial-resistant) pasteurella pneumonias. It has occurred following a course as short as 7 days with a dosage as low as 5 mg per pound of body weight administered twice daily by intramuscular injection. It may be prudent to limit the course of systemic therapy with neomycin to 4 days or less. Sulfonamide nephrotoxicosis results from drug crystal formation within the renal tubules. Since crystal formation occurs primarily in acidic urine, and since bovine urine is nearly always basic, the condition occurs only rarely in cattle.

Ototoxicosis occurs only after prolonged systemic therapy with an aminoglycoside[2] (Table 22). Auditory ototoxicosis would be of little economic importance in cattle. Vestibular ototoxicosis is rarely, if ever, reported in cattle.

Neuromuscular blockade may result from administration of an aminoglycoside or polymyxin antimicrobial into the pleural or peritoneal cavity or by rapid intravenous injection, so that a high plasma concentration is rapidly

TABLE 17. Antimicrobials Eliminated by a Combination of Renal and Biliary Excretion.

Erythromycin
Tylosin
Tetracyclines

TABLE 18. Antimicrobials Eliminated by a Combination of Hepatic Metabolism and Renal Excretion.

Sulfonamides
Trimethoprim

TABLE 19 Antimicrobials Eliminated Entirely by Biliary Excretion.

Lincomycin

TABLE 20. Antimicrobials Which Are Destroyed or Inactivated in an Acidic Environment.

Penicillin G
Aminoglycosides
Dihydrostreptomycin
Neomycin
Kanamycin
Gentamicin
Macrolides
Erythromycin
Tylosin
Lincomycin

attained.[2] The result is complete paralysis, including respiratory paralysis. This event is reversible with calcium gluconate or neostigmine, when caused by an aminoglycoside. When caused by polymyxins, calcium gluconate is effective but neostigmine is not.[2] This problem may also result from repeated administration of these drugs by subcutaneous or intramuscular routes to animals with renal failure (since these drugs are eliminated by renal excretion).

Fatal chloramphenicol toxicosis, associated with impaired glucose metabolism, has been reported in newborn calves treated repeatedly with chloramphenicol.[9] The precise mechanism of this toxicosis is unknown. Chloramphenicol is eliminated mainly by hepatic metabolism.[3] The responsible hepatic enzyme systems are not fully functional in the newborn calf[3], resulting in delayed chloramphenicol elimination (Table 23). If chloramphenicol is used in calves less than 7 days of age, it is suggested that the recommended dosage (Table 2) not be administered more frequently than at 4-day intervals.

10. The withdrawal period required prior to slaughter.

Recommended withdrawal periods are summarized (Tables 1 and 2). No firm recommendation is possible when any drug is used in a dosage or administered by a route that is not approved by the FDA. It should be kept in mind that aminoglycoside antibiotics may be found in the kidney of cattle for several months after therapy is terminated and may result in a drug residue violation.

TABLE 21. Nephrotoxic Antimicrobials.

Cephaloridine*
Aminoglycides*, **
Neomycin
Gentamicin
Tobramycin
Amikacin
Kanamycin
Streptomycin
Sulfonamides
Polymyxin B*
Methicillin

*Concurrent administration enhances nephrotoxicity.
**In order of relative nephrotoxicity.

TABLE 22. Antimicrobials Associated with Ototoxicosis.

Vestibular Damage	Auditory Damage
Streptomycin	Dihydrostreptomycin
Gentamicin	Amikacin
	Kanamycin
	Neomycin

TABLE 23. The Half-life of Chloramphenicol in the Bovine as Influenced by Age.

Age	Half-life (hrs.)
1-day	14.6
7-days	6.5
10-12 weeks	4.8
Adult	4.0

TABLE 24. Bacteriostatic Antimicrobial Agents.

Sulfonamides
Tetracyclines
Macrolides
Erythromycin
Tylosin
Chloramphenicol
Lincomycin
Spectinomycin
Trimethoprim

Other considerations which should be remembered when treating bacterial infections are as follows:

1. *Simultaneous use of corticosteriods and bacteriostatic antimicrobials (Table 24) is contraindicated:*

The influx of neutrophils and other phagocytes to the area of infection is essential to clearance of bacteria from the lesion, and is suppressed by administration of corticosteriods.[3,5]

2. *The dosage of an antimicrobial drug required for effective treatment of a bacterial infection is proportional to the magnitude and severity of the bacterial infection.*

When massive numbers of bacteria are present within a lesion, a concentration of drug in excess of the *in vitro* MIC of the drug for that organism may be necessary for effective controls.[2,5] Consequently, when treating life-threatening bacterial infections in man, it is recommended that that plasma antimicrobial concentrations which are 5 to 10 times the MIC value for the infecting organism be maintained.[2] High plasma concentrations also accelerate and facilitate drug penetration across cellular membranes and into necrotic tissues.[3]

3. *When treating with penicillin G, it may not be essential to maintain continuously inhibitory drug concentrations in the plasma and bacterial environment.*

Penicillins, cephalosporins and vancomycin kill bacteria by inhibiting the transpeptidation enzyme reaction which is necessary for normal cell wall synthesis.[5] Susceptible bacteria exposed to these drugs produce a defective, "leaky" cell wall, water is absorbed into the bacterial cytoplasm, and swelling and lysis result. Because the "poisoned" enzyme system does not recover

for 8 to 12 hours after removal from the influence of penicillin G, intermittently inhibitory plasma penicillin G concentrations (and presumably those of other penicillins, cephalosporins and vancomycin) may be as effective as continuously inhibitory concentrations.[10,11]

Combined Antimicrobial Therapy

Combined antimicrobial therapy is defined as the simultaneous use of 2 antimicrobial agents. Indications for combined antimicrobial therapy are as follows:

1. *For treating chronic infections so as to delay the emergence of resistant mutants:*[2]
   This is mainly a consideration when treating chronic infections in man, such as tuberculosis, (where treatment must be continued for months or years).
2. *For treating mixed infections not sensitive to the same antimicrobial:*
   This is an important indication for combined therapy in beef cattle practice. Mixed lung infections with 2 pasteurella strains or with a pasteurella and a *C. pyogenes* not sensitive to the same drug are a frequent occurrence.
3. *For treatment of life-threatening infections, before the results of laboratory studies are available:*
   When treating bacterial infections in commercial cattle, without benefit of antimicrobial susceptibility data for the infecting bacterium, it has been recommended that treatment with a second antimicrobial drug should be initiated whenever a favorable response to treatment with the initial antimicrobial drug has not been observed within 48 hours.[1,12] However, should treatment of a seriously ill animal be initiated with a drug to which the infecting bacterium is resistant, the animal may be beyond help by the time it can be recognized that the treatment is ineffective. Combined therapy may be desirable in these cases, in order to reduce the likelihood that antimicrobial resistance will be encountered.
4. *To achieve additive or synergistic effects against the infecting bacterium:*

Possible Effects of Combined Therapy Against a Single Strain of an Infecting Bacterium

There are 4 possible effects that may be observed when combined therapy is utilized: indifference, antagonism, addition and synergism:

1. *Indifference:* The combined effect is no greater than that of the more effective drug.
2. *Antagonism:* Antagonism results when a cell wall-active bactericidal drug (penicillins, cephalosporins or vancomycin) is used in combination with a bacteriostatic drug (Table 24). Should the bacteriostatic drug effectively inhibit bacterial growth, defective bacterial cell wall will not be produced, and the bactericidal activity of the cell wall-active drug will be antagonized.[2] Antagonism is of primary importance when treating bacterial endocarditis, a disease in which all infecting bacteria must be killed in order to effect a permanent cure. In the experience of the author, bactericidal drugs (Table 25) are no more effective than are bacteriostatic drugs (Table 24) for treatment of the economically-important bacterial diseases of cattle. If replication can be stopped, the bacteria will be rapidly eliminated by phagocytes. Combined therapy, with a bacteriostatic drug to which the infecting organism is resistant, does not result in antagonism. The author's field records indicate that feedlot calves with severe bronchopneumonia respond as well to combined therapy with

TABLE 25. Bactericidal* Antimicrobial Agents.

Penicillins
Penicillin G
Ampicillin
Cloxacillin
Amoxycillin
Aminoglycosides
Dihydrostreptomycin
Neomycin
Kanamycin
Gentamicin
Polymyxins
Cephalosporins
Trimethoprim - Sulfonamide preparations
Nitrofurans
Bacitracin

*Lethal at or near the minimal inhibitory concentration.

TABLE 26. Response Rates in Previously Unmedicated Holstein Steer Calves Treated for Acute Bacterial Pneumonia in a Feedlot Environment* Using a Bacteriostatic Drug or a Combination of a Bactericidal Drug and a Bacteriostatic Drug.

Treatments Utilized	Severity of infection	No. of calves treated	No. of calves responding favorably (treatment could be terminated)
Sulfamethazine, U.S.P.**	Average	407	318 (78.1)[a]
Sulfamethazine, U.S.P.** plus Procaine penicillin G, aqueous suspension +	Severe	191	150 (78.5)[a]

*Between 11/16/77 and 8/15/78. **Administered orally in bolus form using a loading dose of 1.5 Grains/pound of body weight and a maintenance dose of 1 Grain/pound of body weight, once daily. +Administered once daily by subcutaneous injection in a dose of 30,000 units/pound of body weight. [a]Percent.

sulfamethazine-procaine penicillin G as do calves with less severe bronchopneumonia treated with sulfamethazine alone (Table 26). The problem of antagonism appears to have been over-emphasized by pharmacologists.

3. *Addition:* Here the combined action is equivalent to the sum of each antimicrobial drug used alone. This interaction has the effect of increasing drug dosage, i.e.: increased margin of safety in massive infections and increased rate of cellular membrane penetration.
4. *Synergism:* When synergism occurs, the combined effect is greater than the sum of each drug used alone. The best example in veterinary medicine is the synergistic effect of a trimethoprim-sulfonamide combination. The synergistic effect from this combination results from inhibition of 2 sequential steps in bacterial synthesis of tetrahydrofolate.[2] Dramatic synergistic effects are observed against a wide variety of bacterial species. Synergism is even observed, with this combination, in instances where a bacterium is resistant to both drugs used alone. Unfortunately, trimethoprim is rapidly metabolized by the liver in cattle old enough to have a functional rumen.[3] The combination has potential value, however, in the pre-ruminant calf.

Cell wall-active drugs (such as penicillins, cephalosporins and vancomycin), when used in combination with an aminoglycoside antibiotic, sometimes result in marked synergistic bactericidal activity. The cell wall-active drug may facilitate penetration of an aminoglycoside through the bacterial cell wall, resulting in enhanced bactericidal activity from the aminoglycoside.[2] No combination of any cell wall-active drug and any aminoglycoside drug is uniformly synergistic against all species of bacteria or even against all strains of the same species, however. The phenomenon has been observed mainly with enterococci and *Listeria monocytogenes.*[3] A combination of carbenicillin and gentamicin has been shown to be synergistic against certain strains of *Pseudomonas aeruginosa.*[3]

References

1. Hjerpe, C.A., and Routen, T.A.: Practical and Theoretical Considerations Concerning Treatment of Bacterial Pneumonia in Feedlot Cattle, with Special Reference to Antimicrobic Therapy. Proc. 9th Ann. Conv. AABP, San Francisco, 1976. p. 97. 2. Roberts, R.B.: Antimicrobial Therapy. In: Textbook of Medicine. 14th ed., Beeson, P.B., and McDermott, W., eds., p. 459. W.B. Saunders Co., Philadelphia, Pa., 1975. 3. Baggot, J.D.: Systemic Antimicrobial Therapy in Large Animals. In: The Pharmacologic Basis of Large Animal Practice. Bogan, J., and Lees, P., eds. Blackwell Scientific Publications, Oxford, 1983. 4. Stowe, C.M.: The Sulfonamides. In: Veterinary Pharmacology and Therapeutics. 3rd ed., Jones, L.M., ed., p. 458. Iowa State Univ. Press, Ames, Iowa, 1965. 5. Jawetz, E., Melnick, J.L., and Adelberg, E.A.: Review of Medical Microbiology, 12th ed., p. 112. Lange Medical Publications, Los Altos, Calif., 1976. 6. Hjerpe, C.A., Davis, Ca.: Unpublished data, 1982. 7. Ling, G.V.: Choice of Antimicrobial Agents in the Treatment of Urinary Tract Infections, In: Current Veterinary Therapy VII—Small Animal Practice. Kirk, R.W., ed., p. 1162. W.B. Saunders Co., Philadelphia, Pa., 1980. 8. Huber, W.G.: Chloramphenicol and Other Antimicrobial Substances. In: Veterinary Pharmacology and Therapeutics. 3rd ed., Jones, L.M., ed. p. 539. Iowa State Univ. Press, Ames, Iowa, 1965. 9. Huffman, E.M., Clark, C.H., Olson, J.D., and Ball, L.: Serum Chloramphenicol Concentrations in Preruminant Calves: A Comparison of Two Formulations Dosed Orally. J. Vet. Pharmacol. Therap. 4 (1981) 225. 10. Weinstein, L., and Daikos, G.: The Treatment of Scarlet Fever with Crystalline Penicillin G Administered Orally or Parenterally Twice a Day. Am. Pract. Digest Treat. 2 (1951) 60. 11. Weinstein, L., and Perrin, T.: Treatment of Scarlet Fever with Penicillin G Administered Orally Three Times a Day. J. Pediat. 37 (1950): 844. 12. Hjerpe, C.A.: Treatment of Bacterial Pneumonia in Feedlot Cattle. Proc. 8th Ann. Conv. AABP, Atlanta, 1975. p. 33.