Antimicrobial selection, administration and dosage

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ABSTRACT

Various types of information contribute to the selection of an antimicrobial agent. Initial requirements are diagnosis of the site and nature of the infection, assessment of the severity of the infectious process and medical condition of the diseased animal; these are embodied in clinical experience. Additional considerations include identification of the causative pathogenic microorganism, knowledge of its susceptibility to antimicrobial agents (microbiological considerations) and of the pharmacokinetic properties of the drug of choice and alternative drugs, and their potential toxicity (pharmacological considerations) in the animal species. Select an antimicrobial drug and dosage form appropriate for use in the particular animal species. Usual dosage regimens may be applied, except in the presence of renal or hepatic impairment, when either modified dosage or a drug belonging to another class should be used. The duration of therapy is determined by monitoring the response both by clinical assessment and bacterial culture. A favourable clinical response is the ultimate criterion of successful therapy.

Key words: animal therapy, antimicrobial selection, dosage.

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INTRODUCTION

For the treatment of a bacterial infection, the antimicrobial agent selected must have activity against the causative pathogenic microorganism and must attain effective concentrations at the site of infection. The ultimate criterion of successful therapy is a favourable clinical response to the treatment. Such a response depends on the interrelations between the causative pathogenic microorganism the antimicrobial drug selected and dosage used, and the animal receiving treatment. Inadequacy of host defense mechanisms, particularly in neonatal foals and in immuno-compromised animals, could contribute to a discrepancy between the expected and actual response to antimicrobial therapy. In these animals, it is preferable to use antimicrobial agents, alone or combined, that produce a bactericidal effect.

ANTIMICROBIAL CLASSIFICATION

Antimicrobial agents are classified on the basis of molecular structure, which determines their chemical nature and related physico-chemical properties (pK_a/pH-dependent degree of ionisation, lipid solubility). The drugs within each class generally have the same mechanism of action, a broadly similar spectrum of antimicrobial activity (Table 1) and reasonably similar disposition (*i.e.* extent of distribution and elimination processes) (Table 2). Individual drugs within a class differ quantitatively in antimicrobial activity and, when mainly eliminated by hepatic metabolism, in the rate of elimination (usually expressed as half-life). Bioavailability, which refers to the rate and extent of absorption, and the withdrawal period, vary with the dosage form of a drug and may differ between animal species. Selective tissue binding (*e.g.* aminoglycosides) is a cause for concern in terms of the pathological lesion that may be produced in the particular tissue and the persistence of drug residues (a long withdrawal period is required).

MECHANISMS OF ACTION

Antimicrobial action usually depends on the inhibition of biochemical events that exist in or are essential to the bacterial pathogen but not the host animal. Unfortunately, the action of antimicrobial agents is not selective for pathogenic microorganisms and the balance between the commensal flora can be seriously disturbed, particularly in the colon of horses (doxycycline, macrolides and lincosamides).

The actions of antimicrobial agents can be adequately distinguished by the following general mechanisms:

(i) Selective inhibition of bacterial cell wall synthesis (penicillins, cephalosporins, bacitracin, vancomycin). Following attachment to receptors (penicillin-binding proteins), beta-lactam antibiotics inhibit transpeptidation enzymes and thereby block the final stage of peptidoglycan synthesis. This action is followed by inactivation of an inhibitor of autolytic enzymes in the bacterial cell wall. Bacitracin and vancomycin inhibit early stages of peptidoglycan synthesis.

(ii) Inhibition of cell membrane function by disrupting functional integrity of the bacterial (polymyxins) or fungal (antifungal azoles and polyenes) cytoplasmic membrane. Antifungal azoles (*e.g.* ketoconazole, miconazole, fluconazole) act by inhibiting the biosynthesis of fungal membrane lipids, especially ergosterol. Polyenes (*e.g.* amphotericin B, natamycin) require ergosterol as a receptor in the fungal cell membrane in order to exert their effect; this sterol is absent from the bacterial cell membrane. Polyene antibiotics and the synthetic antifungal azoles act on fungi, whereas the polymyxins act on gram-negative bacteria.

(iii) Inhibition of protein synthesis through an action on certain subunits of microbial ribosomes (aminoglycosides, tetracyclines, chloramphenicol and its derivatives, macrolides and lincosamides). Each class of antimicrobial agent attaches to a different receptor site, apart from macrolides and lincosamides, which bind to the same site on the 50S subunit of the microbial ribosome.

(iv) Inhibition of nucleic acid synthesis. Fluoroquinolones block the action of DNA gyrase; rifampin binds strongly to DNA-dependent RNA polymerase; metronidazole, following chemical reduction of the nitro group of the molecule within anaerobic bacteria or sensitive protozoal cells, produces a bactericidal effect by reacting with various intracellular macromolecules.

(v) Inhibition of folic acid synthesis in susceptible microorganisms and ultimately the synthesis of nucleic acids.

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Table 1: **Spectrum of antimicrobial activity** (semi-quantitative).

Antimicrobial class	Usual effect[a]	Gram-positive	Gram-negative	Anaerobic bacteria	Other microorganisms
Penicillins[b]	C				
Penicillin G		+++	(+)	+(+)	–
Aminobenzyl-penicillin		++	+(+)	+	–
Carboxy-penicillin		+	+(+)	+	–
Isoxazolyl-penicillin		++	–	–	–
Cephalosporins[c]	C				
1st generation		++	+	+	–
2nd generation		+	++	++(cefoxitin)	–
3rd generation		+	++(+)	+(ceftizoxime)	–
Aminoglycosides	C	(+)	+++	–	(*Mycoplasma* spp.)
Fluoroquinolones	C	+(+)	+++	–	*Mycoplasma* spp. *Chlamydia* spp.
Trimethoprim/sulphonamide	C	++	++	+	*Chlamydia* spp.
		Protozoa: *Toxoplasma* spp.			
Tetracyclines	S	++	++	+	*Mycoplasma* spp. *Chlamydia* spp. *Rickettsia* spp.
		Protozoa: *Theileria* spp., *Eperythrozoon* spp., *Anaplasma* spp.			
Chloramphenicol	S	++	+(+)	++	(*Mycoplasma* spp.) (*Chlamydia* spp.) *Rickettsia* spp.
Macrolides	S	++	(+)	(+)	*Mycoplasma* spp. (Tylosin)
Lincosamides	S	++	–	++(clindamycin)	(*Mycoplasma* spp.)
Rifampin	C	++	–/(+)	+(+)	*Chlamydia* spp. *Rickettsia* spp.
Metronidazole	C	–	–	+++	–
		Protozoa: *Trichomonas foetus, Giardia lamblia, Histomonas meleagridis*			
Sulphonamides	S	+	(+)	+	*Chlamydia* spp.

[a]C = bactericidal; S = bacteriostatic.
[b]**Penicillins**
Penicillin G: phenoxymethyl penicillin (penicillin V) – acid-stable.
Aminobenzyl penicillins: ampicillin, amoxillin and pro-drugs.
Carboxypenicillins: ticarcillin, carbenicillin – anti-pseudomonal (*P. aeruginosa*).
Isoxazolyl penicillins: cloxacillin, oxacillin, nafcillin, methicillin – relatively resistant to staphylococcal beta-lactamase; acid-stable.
[c]**Cephalosporins**
1st generation: cefadroxil, cephalexin (both oral); cefazolin, cephalothin (both parenteral).
2nd generation: cefuroxime (oral); cefoxitin (IV).
3rd generation: cefixime (oral).
Cefotaxime, ceftizoxime, cefoperazone, ceftriaxone, ceftazidime (all IV).

By competing with para-aminobenzoic acid (PABA) for the enzyme dihydropteroate synthetase, sulphonamides prevent the incorporation of PABA into dihydrofolate, while trimethoprim, by selectively inhibiting dihydrofolate reductase, prevents the reduction of dihydrofolate to tetrahydrofolate (folic acid). Animal cells, unlike bacteria, utilise exogenous sources of folic acid. Pyrimethamine inhibits protozoal dihydrofolate reductase, but is less selective for the microbial enzyme and therefore more toxic than trimethoprim to mammalian species.

Knowledge of the mechanisms of action of antimicrobial agents is required for understanding resistance acquired through chromosomal mutation and selection, and forms the basis of selecting antimicrobials for concurrent use, either as combination preparations or separately.

ANTIMICROBIAL RESISTANCE

There are many different mechanisms whereby microorganisms might exhibit resistance to antimicrobial drugs. Inherent and acquired resistance to an antimicrobial agent are clearly distinguishable and due to different mechanisms, although lack of a favourable clinical response (therapeutic failure) is the invariable outcome.

Inherent resistance

Inherent resistance largely limits the spectrum of activity of an antimicrobial agent, while acquired resistance invariably decreases the quantitative susceptibility of pathogenic microorganisms.

In order to reach receptors (penicillin-binding proteins), beta-lactam

Table 2: **Extent of distribution and processes of elimination of antimicrobial agents.**

Antimicrobial agent	Extent of distribution (comment)	Elimination process(es)[a]
Beta-lactams	Limited – low intracellular concentrations	E (r), except nafcillin, cefoperazone and ceftriaxone, E(r+h)
Aminoglycosides	Limited – mainly ECF (selective binding to renal cortex; inner ear)	E(r)
Fluoroquinolones	Wide (developing cartilage)	M(h) + E(r+h)
Trimethoprim	Wide	M(h) + E(r)
Sulphonamides	Moderate	M(H) + E(r), except sulfisoxazole, E(r) + M(h)
Tetracyclines	Wide (sites of ossification; developing teeth)	E(r+h), except doxycycline, E(f)
Chloramphenicol[b]	Wide	M(h) + E(r)
Metronidazole[b]	Wide	M(h) + E(r)
Erythromycin[b]	Wide – high intracellular concentration	M(h) + E(h)
Clindamycin	Wide	M(h) + E(r)
Rifampin[c]	Wide – high intracellular concentration, including phagocytes	M(h) + E(h+r)

[a]E(r) = excretion (renal); M(h) = metabolism (hepatic); E(r+h) = excretion (renal and hepatic in bile); E(f) = excretion (in faeces).
[b]Inhibits hepatic microsomal enzymes.
[c]Induces hepatic microsomal enzymes.

antibiotics must penetrate the outer layers of the bacterial cell envelope. Inherent resistance of many gram-negative bacteria to penicillin G (benzylpenicillin) is due to low bacterial permeability, lack of penicillin-binding proteins and/or a wide variety of beta-lactamase enzymes. Gram-negative bacteria have an outer phospholipid membrane that may hinder passage of beta-lactam antibiotics. Some (such as ampicillin and amoxicillin) pass through pore molecules in this outer barrier more readily than penicillin G. Owing to their higher capacity to penetrate cell membranes, 3rd-generation cephalosporins (except cefoperazone) have activity against an expanded range of gram-negative aerobic bacteria and reach infection sites in the central nervous system. Streptococci have a natural permeability barrier to aminoglycosides. Their penetrative capacity can be enhanced by the simultaneous presence of a cell wall-active drug, such as a penicillin.

Most gram-negative aerobic bacteria, with the notable exception of *Brucella* spp., are relatively impermeable and therefore inherently resistant to rifampin; the site of action of rifampin is intracellular. Microbial susceptibility to tetracyclines depends on the attainment of high intracellular drug concentrations. Individual tetracyclines differ in lipid solubility. A distinction must be made between microorganisms that have low capacity for penetration by tetracyclines (inherently resistant) and those that acquire resistance through defective active transport of these drugs across the inner cytoplasmic membrane. Since mycoplasmas are bounded by a triple-layered 'unit membrane' and lack a rigid cell wall, these microorganisms are inherently resistant to beta-lactam antibiotics. The inherent resistance of aerobic bacteria to metronidazole may be attributed to the absence of an anaerobic environment for activation (chemical reduction of the nitro group) of the drug to take place.

Acquired resistance

The potential for genetic exchange between bacteria, combined with their short generation time, can rapidly lead to resistant bacterial populations. Acquired, genetically based resistance may be due to chromosomal mutation (altered structural target or metabolic pathway essential for antimicrobial action) or, more importantly, the acquisition, by bacterial conjugation, of resistance (R) plasmids[16]. Resistance plasmids (transferable genetic material) may be present in bacteria as extrachromosomal circular DNA molecules that replicate independently of, but synchronously with, chromosomal DNA. Plasmid genes for antimicrobial resistance often control the formation of bacterial enzymes that are capable of either inactivating antimicrobial agents or decreasing bacterial membrane permeability to antimicrobials[11].

Plasmid-mediated resistance to penicillins and cephalosporins (beta-lactam antibiotics) is due to the formation of beta-lactamase enzymes by *S. aureus* or enteric gram-negative rods. Some beta-lactamases can be firmly bound by compounds such as clavulanic acid (combined with amoxycillin or ticarcillin) and sulbactam (combined with ampicillin) and can thus be prevented from attacking hydrolysable penicillins. Gram-positive bacteria, apart from staphylococci, generally lack the ability to acquire R plasmids.

Gram-negative bacteria that are resistant to aminoglycosides produce enzymes that inactivate drugs in this class, apart from amikacin, by adenylation, acetylation or phosphorylation. This type of resistance is usually plasmid-mediated. Plasmids code for the enzyme acetyltransferase that inactivates chloramphenicol. Florfenicol, an analogue of thiamphenicol, is less susceptible than chloramphenicol to inactivation by bacterial acetyltransferase. Defective active transport of tetracyclines across the inner cytoplasmic membrane of microorganisms that have acquired resistance may be plasmid-mediated. Since the plasmid genes that code for tetracycline resistance are closely associated with those for chloramphenicol and aminoglycosides (especially streptomycin), multiple drug resistance may result. Multiple drug-resistance plasmids, which commonly occur in Enterobacteriaceae such as *Salmonella, E. coli* and *Proteus,* will be maintained in a population by the use of any antibiotic to which resistance is encoded by the plasmid genes.

The spread of multiple drug resistance has serious implications on account of its persistence. Plasmid-mediated resistance to lincosamides and macrolides is the result of methylation of the shared receptor site on the 50S subunit of the bacterial ribosome. Plasmid-transferable resistance has recently been reported for fluoroquinolones[13].

Chromosomal mutants are commonly resistant by virtue of a change in a structural receptor for an antimicrobial agent. Resistance to beta-lactam antibiotics (penicillins and cephalosporins) may be attributed to the loss (or alteration) of penicillin-binding proteins. Chromosomal resistance to aminoglycosides (including amikacin) is associated with the deletion (or alteration) of a specific receptor (protein) on the 30S ribosomal subunit. Resistance to fluoroquinolones (especially in coagulase-positive staphy-

Table 3: **Empirical antimicrobial drug selection based on knowledge of pathogenic microorganism.**

Microorganism	Drug of choice	Alternatives
Gram-positive aerobic bacteria		
Streptococcus spp.	Penicillin G	1st-generation cephalosporin: trimethoprim/sulphonamide
Staphylococcus, non-penicillinase-producing	Penicillin G	1st-generation cephalosporin
Staphylococcus, penicillinase-producing	Isoxazolyl penicillins	1st-generation cephalosporin; fluoroquinolone; amoxycillin/clavulanate
Staphylococcus, methicillin-resistant	Fluoroquinolone	Trimethoprim/sulphonamide
Bacillus spp.	Penicillin G	Erythromycin
Erysipelothrix rhusiopathiae	Penicillin G	Erythromycin
Corynebacterium spp.	Penicillin G	Erythromycin
Listeria monocytogenes	Aminobenzyl-penicillin	Chloramphenicol; trimethoprim/sulphonamide
Nocardia spp.	Trimethoprim/sulphonamide	Minocycline (± sulphonamide)
Mycobacterium tuberculosis	Rifampin + isoniazid	Streptomycin
Gram-negative aerobic bacteria		
Coliforms (*E. coli, Klebsiella* spp., *Proteus* spp., *enterobacter* spp.)	Gentamicin (or amikacin)	Fluoroquinolone; 3rd-generation cephalosporin
Salmonella spp.	Trimethoprim/sulphonamide	Fluoroquinolone; aminobenzyl-penicillin
Pasteurella multocida	Aminobenzyl-penicillin	Aminoglycoside; fluoroquinolone
Actinobacillus spp.	Trimethoprim/sulphonamide	Fluoroquinolone; amoxycillin/clavulanate; tetracycline
Leptospira spp.	Aminobenzyl-penicillin	Erythromycin; streptomycin
Helicobacter spp.	Erythromycin	Fluoroquinolone
Bordetella bronchiseptica	Tetracycline	Trimethoprim/sulphonamide; chloramphenicol; gentamicin
Pseudomonas aeruginosa	Gentamicin ± ticarcillin (or carbenicillin)	Ciprofloxacin; 3rd-generation cephalosporin
Moraxella bovis	Oxytetracycline	Cephalothin; chloramphenicol; aminoglycoside
Anaerobic bacteria		
Clostridium spp.	Penicillin G	1st-generation cephalosporin; (clindamycin)
Actinomyces spp.	Penicillin G	Erythromycin; trimethoprim/sulphonamide
Fusobacterium spp	Metronidazole	Penicillin G; clindamycin; 1st-generation cephalosporin
Bacterioides spp. (other than *B. fragilis*)	Metronidazole	Penicillin G; clindamycin; cefoxitin
Bacterioides fragilis	Metronidazole or clindamycin	Chloramphenicol; ampicillin/sulbactam; cefoxitin
Other microorganisms		
Mycoplasma spp.	Tylosin or tiamulin	Fluoroquinolone; tetracycline
Chlamydia spp.	Tetracycline	Trimethoprim/sulphonamide
Rickettsia spp.	Tetracycline	Chloramphenicol

lococci and *Pseudomonas* spp.) may be due to mutation of the target enzyme, DNA gyrase. The rapid development of high-level resistance to rifampin, associated with its use as the sole antimicrobial agent, results from chromosomal mutation of bacterial RNA polymerase. In sulphonamide-resistant mutants the affinity of dihydropteroate synthetase for p-aminobenzoic acid may exceed that for sulphonamide, which is a reversal of the situation in sulphonamide-sensitive microorganisms. At least some sulphonamide-resistant bacteria can, like mammalian cells, utilise preformed folic acid for nucleic acid synthesis.

Significance of transferable drug resistance

Acquired resistance to several antibiotics is of particular concern in Enterobacteriaceae and is increasingly found in non-enteric gram-negative bacterial pathogens, as well as in the commensal flora. A causal relationship has been shown between the use of antimicrobials and the development of resistance. The use of antimicrobials does not induce resistance but rather provides an intense selection pressure that, by destroying the susceptible bacteria in the host animal, allows the resistant bacteria to proliferate[9]. The gravity of this adverse situation lies in the fact that, once developed, multi-resistant organisms can persist in the individual or exposed animal population and in the environment. The control of antimicrobial resistance, in so far as is possible, depends on the judicious selection and appropriate use of antimicrobial agents.

Cross-resistance

Microorganisms that are resistant to a certain antimicrobial agent may also be resistant to other antimicrobials with the same mechanism of action or share the same receptor-binding site. Cross-resistance mainly applies to antimicrobial agents that are closely related structurally, *i.e.* are within the same class (*e.g.* aminoglycosides, fluoroquinolones, lincosamides, sulphonamides, chloramphenicol and its derivatives). Since all tetracyclines have the same basic structure, cross-resistance between tetracyclines is to be expected. Although lincosamides and macrolides are structurally unrelated, they share the same receptor-binding site, have the same mechanism of plasmid-mediated resistance, and cross-resistance between drugs in these 2 classes is common. Because of its unique action (inhibition of RNA polymerase), cross-resistance between rifampin and other antimicrobial agents does not occur.

APPROACH TO THERAPY

Having diagnosed the presence of a bacterial infection, appropriate specimens should be properly collected to identify the causative pathogenic microorganism(s) and, when considered necessary, to determine its susceptibility. Perform immediate examination of the specimen, including (whenever feasible) a Gram-stained direct smear. The value of immediate examination of clinical specimens in the initial selection of an antimicrobial agent cannot be

Table 4: **Suggested guideline for the interpretation of MIC** (µg/mℓ) **of various antimicrobial agents based on bacterial isolates of equine origin, apart from fluoroquinolones which relate to isolates of canine origin.**

Antimicrobial agent	Susceptible	Moderately susceptible	Resistant
Penicillin G	≤0.125	0.25–16	>16
Ampicillin	≤1	2–16	>16
Amoxycillin	≤1	2–16	>16
Gentamicin	≤2	4–8	>8
Amikacin	≤4	8–16	>16
Fluoroquinolones[a]	≤1	2–4	>4
Erythromycin	≤0.5	1–4	>4
Tetracycline	≤1	2–4	>4
Chloramphenicol	≤4	8–16	>16
Trimethoprim/sulfamethoxazole	≤0.5/10	1/20–2.5/50	>3/75

[a]Quantitative susceptibility of bacterial pathogens varies between individual fluoroquinolones, *e.g.* the minimum inhibitory concentration of ennofloxacin for the majority of susceptible *E. coli* strains isolated from calves is 0.25 µg/mℓ.

Table 5: **Usual dosage for antimicrobial preparations used in dogs and cats.**

Drug preparation	Route of administration	Dosing rate	
		Dose (mg/kg)	**Interval** (h)
Penicillin G, sodium	IV,IM,SC	20 000–40 000 IU/kg	4–6
Penicillin G, procaine	IM, SC	25 000 IU/kg	24
Penicillin V, calcium	PO	10–20	8
Ampicillin sodium	IV, IM, SC	10–20	8
Ampicillin	PO	25	8
Hetacillin or pivampicillin	PO	20–30	8
Amoxycillin trihydrate	PO	12.5–25	8–12
Amoxycillin trihydrate/clavulanate, potassium	PO	12.5–25	8–12
Cloxacillin sodium	PO	25–35	8
Cefadroxil	PO	20–30	8–12
Cephalexin monohydrate	PO	20–30	8–12
Cefazolin sodium	IV	10–20	8
Gentamicin sulphate	IM/SC	3–5	8–12 (dogs) (12–24 cats)
Amikacin sulphate	IM/SC	6–10	8–12
Enrofloxacin	PO	5–10	12
Marbofloxacin	PO	2–4	24
Trimethoprim/sulphadiazine	PO	5/25	12
Trimethoprim/sulphamethoxazole	PO	5/25	12
Tetracycline hydrochloride	PO	20	8
Oxytetracycline hydrochloride	PO	20	12
Oxytetracycline dihydrate	PO	40	12
Doxycycline hydrochloride	PO	5	12
Chloramphenicol	PO	25	8 (dogs) 12 (cats)
Chloramphenicol palmitate	PO	25	8 (dogs)
Metronidazole	PO	10–20	8–12
Erythromycin	PO	10–20	8–12
Erythromycin estolate	PO	10–20	8–12
Clindamycin hydrochloride	PO	5–10	8–12
Sulfisoxazole	PO	50	8
Sulfasalazine	PO	25	8 (dogs)
Ketoconazole	PO	5–10	12–24
Griseofulvin (micronised)	PO	25–50	12–24

overemphasised.

Blood culture is a valuable, although not invariably certain, technique for making a microbiological diagnosis of septicaemia in neonatal foals.

Initial (empirical) treatment

Since there will be some delay in obtaining laboratory results, antimicrobial therapy should be initiated on an informed empirical basis. The choice of drug for initial therapy is largely based on clinical experience, the nature (and site) of the infectious disease process and epidemiological pattern in the herd or geographical region, but should be

supported by the findings of specimen examination. A suggested choice of drug for initial therapy, based on knowledge (although tentative at this stage) of the pathogenic microorganism, is presented in Table 3. While the drug of choice presented in this table is generally applicable, selection of the antimicrobial agent must be related to the site of the infection, the animal species and the readily available dosage forms.

Provide supportive measures that would complement antimicrobial effectiveness and assist recovery of the animal from the infection. In neonatal animals, care must be taken to avoid a too-rapid rate of intravenous fluid administration. Fever may serve a useful purpose in infectious diseases and the change in body temperature may be used to assess the progress of the infection. In the presence of an infectious disease, the only indication for an antipyretic drug, *e.g.* aspirin or paracetamol (acetaminophen) in dogs but not in cats, or dipyrone or sodium salicylate administered intravenously to horses, is to decrease body temperature to below a dangerous level, 41 °C (105.8 °F). Concurrent therapy with a non-steroidal, anti-inflammatory drug and an aminoglycoside antibiotic increases the risk of nephrotoxicity. If the infection is suspected to be contagious, isolate the diseased and in-contact animals.

When an appreciable quantity of pus or a foreign body is present, the appropriate surgical intervention is indicated.

Bacterial culture and susceptibility testing

After the pathogenic microorganism has been isolated by bacterial culture (performed under various incubation conditions) and identified, the decision can be made as to whether susceptibility testing (particularly the determination of minimum inhibitory concentration, MIC) is necessary. The susceptibility of certain commonly isolated bacteria is generally predictable. For example, beta-haemolytic Streptococci isolated from horses are susceptible to penicillin G, as are anaerobes, except *Bacterioides* spp. In mixed infections and abscesses, the presence of anaerobic bacteria should always be considered. The fostering of a close working relationship with the clinical microbiology laboratory is important with regard to the relevance of the techniques performed to the clinical situation and the interpretation of the laboratory results.

Concerning susceptibility testing, the disk (agar)-diffusion method is satisfactory only when a microorganism is either very susceptible or very resistant. It should be understood that the method relates antimicrobial drug concentrations achieved in the serum of human beings given usual dosages to the susceptibility pattern of populations of fast-growing aerobic bacteria[15]. The MIC of an organism can be extrapolated from inhibitory zone diameters, and these MIC values have been used to define breakpoints to describe bacteria as susceptible or resistant. The disk-diffusion method provides a qualitative or, at best, semi-quantitative indication of susceptibility, since some antimicrobials become concentrated while others penetrate poorly into certain body fluids and tissues; furthermore, the disposition of many antimicrobial agents differs between human beings and animal species. Owing to the aforementioned limitations of the disk-diffusion method, it is necessary to determine quantitative susceptibility, using the broth dilution method (which measures MIC), of pathogenic microorganisms of frequently unpredictable susceptibility. They include coagulase-positive staphylococci (*S. aureus* and *S. intermedius*) and enteric microorganisms (*E. coli, Klebsiella, Proteus* and *Salmonella* spp.). The determination of quantitative susceptibility could be considered essential for bacteria that have developed multiple drug resistance.

Quantitative susceptibility varies between bacterial genera and species, as well as between strains of a particular species. Moreover, individual drugs within a class differ quantitatively in antimicrobial activity. Tetracyclines might constitute an exception, in that differences in clinical efficacy between tetracyclines are largely attributable to features of bioavailability, distribution and excretion. Suggested interpretative guidelines for MIC breakpoint values are presented (Table 4). The choice of antimicrobial agent for systemic therapy is almost invariably limited to drugs to which the bacterial pathogen is susceptible. For treatment of canine urinary tract infections, the range of antimicrobial agents can be extended to include drugs to which the bacterial pathogen is moderately susceptible provided urinary concentrations exceeding 4 times the MIC could be maintained during therapy.

Knowledge of the susceptibility of a pathogenic microorganism is most useful for selecting the antimicrobial agent of choice and can be applied in tailoring dosage of the drug for an individual animal but, even though *in vitro* susceptibility (particularly MIC) generally correlates well with clinical efficacy, it cannot be relied upon to predict response to therapy. Accumulated data on MIC_{90}, which is the MIC breakpoint value for 90 % of isolates tested, compared over different time periods (*e.g.* on an annual basis), would reveal the pattern of resistance to a drug.

Maintenance therapy

The choice of drug for maintenance therapy rests with the clinician and is based on the severity, site and nature of the infection, knowledge of the susceptibility of the causative pathogenic microorganism and the pharmacokinetic properties of the drug in the animal species, and on clinical experience. Consideration must be given to the toxic potential of the antimicrobial agent of choice, the dosage forms that would be suitable for administration to the individual animal, the ease of repeated administration (which often determines owner compliance), and the overall cost of the likely course of therapy. Due account should be taken of the value, according to the owner, of the animal in making the final choice of antimicrobial agent and the dosage form.

Apply the usual dosage regimen for the drug preparation (dosage form) selected, or apply a dosage regimen tailored to the individual animal and based on the quantitative susceptibility (MIC) of the causative pathogenic microorganism. The latter approach to dosage (specific therapy) assumes greater importance in the treatment of severe systemic infections (such as septicaemia).

Advise the owner regarding supportive measures that should be provided and, in the case of food-producing animals, the specified withdrawal period for the drug preparation selected. The withdrawal period for a drug may vary with the preparation (dosage form) as well as between food-producing animal species. It is stated on the label (and package insert) of authorised drug preparations.

DRUG ADMINISTRATION AND DOSAGE

The route of administration of an antimicrobial drug depends on the site and severity of the infection as well as on the animal species, but is often governed by the dosage forms that are available. It is because bacterial susceptibility (MIC) can be determined *in vitro* and drug disposition processes are quantifiable (in pharmacokinetic terms) that dosing rates for antimicrobial drugs can be calculated. However, various formulations may differ significantly from a standard (reference) formulation in bioavailability of the drug substance (active moiety). Only drug preparations that are bioequivalent in the target species would be expected to have similar clinical efficacy.

Table 6: **Influence of food on the oral bioavailability of antimicrobial agents in dogs and cats.**

Antimicrobial class/preparation	Effect on oral bioavailability[a]
Most penicillins, apart from	↓
amoxycillin and	–
ampicillin pro-drugs	–
Cephalosporins	↓
Fluoroquinolones	–
Trimethoprim/sulphonamide	↓
Most tetracycline, apart from	↓
doxycycline	↑
Chloramphenicol	–
Chloramphenicol palmitate	↑ (cats)
Metronidazole	↑ (dogs)
Erythromycin base	↓
Erythromycin stearate	↓
Erythromycin estolate	↑
Erythromycin ethylsuccinate	↑
Erythromycin enteric-coated formulations	–
Clarithromycin	–
Nitrofurantoin	↑ (dogs)
Ketoconazole	↑
Griseofulvin (micronised)	↑

[a]Oral bioavailability of an antimicrobial agent may vary with formulation of the oral dosage form.

Selected features of the plasma concentration-time profiles are used for bioequivalence assessment of formulations of an antimicrobial agent[12].

Oral administration is used, particularly in dogs and cats, in the treatment of mild and moderate infections or when a prolonged duration of therapy is anticipated (Table 5). The oral bioavailability of many antimicrobial agents is affected by the temporal relationship between feeding and dosing (Table 6). Depending on this relationship, food should either be given 1 h before dosing (*e.g.* with doxycycline, erythromycin estolate, ketoconazole) or be withheld for up to 2 h after dosing (*e.g.* with most penicillins, cephalosporins, tetracyclines, erythromycin base or stearate). The oral bioavailability of some antimicrobial agents (*e.g.* amoxycillin, fluoroquinolones) is indifferent to the time of feeding relative to dosing.

Many of the antimicrobial agents that are given orally to dogs are administered by intramuscular injection, depending on the availability of parenteral preparations, to ruminant animals (Table 7). The systemic availability (extent of absorption) of an antimicrobial agent from a parenteral formulation injected intramuscularly is generally higher when the site of injection is the lateral neck compared with the buttock (*M. semitendineus*)[14,17]. Better antimicrobial absorption from the former injection site could be attributed to wider spread of the parenteral preparation (aqueous suspension or non-aqueous solution) providing greater access to a larger absorptive surface area and possibly to higher blood flow to tissues in this region. At least a portion of the volume injected is more likely to be deposited between muscles (intermuscular), which would facilitate spread of the preparation along fascial planes, in the neck than in the buttock. Even though the usual dosage interval for oxytetracycline dihydrate (a long-acting parenteral formulation) is 48 h, the intramuscular injection of 2 doses (20 mg/kg, 72 h apart) can be recommended for the treatment of infectious bovine keratoconjunctivitis, caused by *Moraxella bovis*[6]. Antimicrobial agents are administered to pigs either in the feed or drinking water, or by intramuscular injection, provided injection site damage is not produced (Table 8). Parenteral preparations should be formulated in a manner such that their intramuscular injection does not cause tissue damage with persistence of drug residues at the injection site. Antemortem methods for evaluating the extent of tissue irritation and rate of resolution at the injection site include the use of ultrasonography[2] and determination of the kinetics of plasma creatine kinase (CK) activity[1,19].

The systemic availability of antimicrobial agents administered orally (pastes) or by nasogastric tube (aqueous suspensions) to horses is significantly decreased by feeding before dosing. Food should be withheld for up to 2 h after drug administration. Metronidazole, which is most useful for the treatment of anaerobic infections (*e.g.* pleuropneumonia, liver abscesses, peritonitis), is an exception in that the drug is well absorbed from the

Table 7: **Usual dosage regimens for antimicrobial preparations used in cattle, sheep and goats.**

Drug preparation	Route of administration	Dosing rate	
		Dose (mg/kg)	**Interval** (h)
Penicillin G, sodium	IV, IM	25 000 IU/kg	6–8
Penicillin G, procaine	IM	25 000 IU/kg	24
Ampicillin sodium	IV, IM	10–20	8
Ampicillin/sulbactam	IM	10	8–12
Amoxycillin trihydrate	IM	10	12
Trimethoprim/sulphonamide	IM	4/20	12
Enrofloxacin	IM	2.5–5	12
Oxytetracycline hydrochloride	IV, IM	10	12
Oxytetracycline dihydrate (long-acting)	IM	20	48
Erythromycin lactobionate	IV, IM	5	8–12
Lincomycin hydrochloride	IM	10	12
Tylosin	IM	20	12
Sulphamethazine (10 % oral solution)	PO	50	12

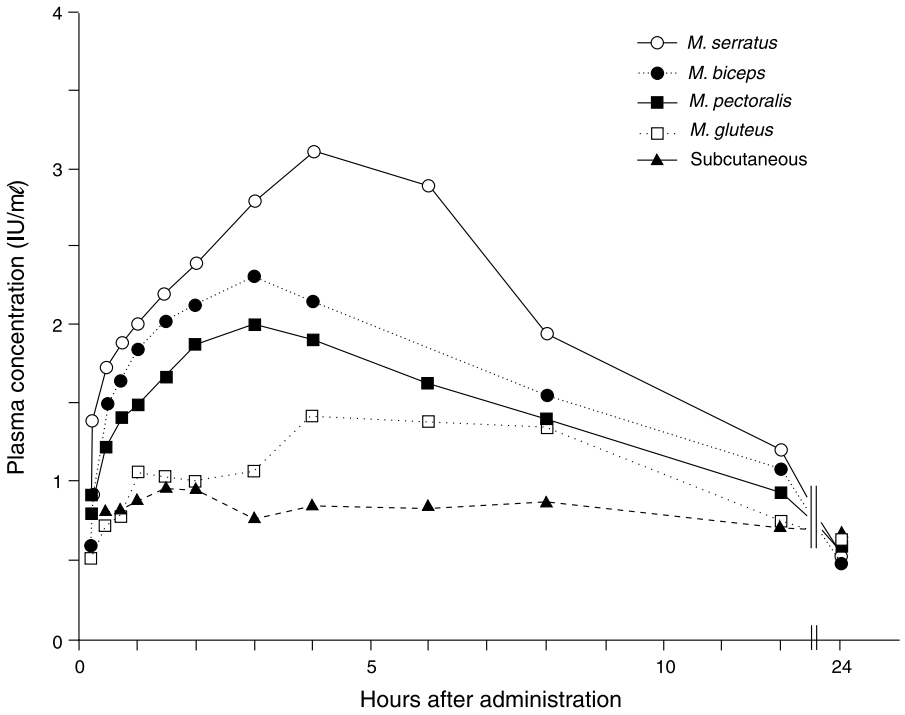

Fig. 1: **Mean plasma penicillin concentration time curves after 20 000 IU procaine penicillin G/kg was administered to five animals** (4 horses, 1 pony) **at five different sites** (after Firth *et al.* 1986[5]).

Table 8: **Usual dosage regimens for antimicrobial preparations used in pigs.**

Drug preparation	Route of administration	Dose (mg/kg)	Interval (h)	Feed (g/US ton)	Water (mg/ℓ)
Ampicillin sodium	IM	10–20	8	–	–
Penicillin G, procaine	IM	20 000 – 40 000 IU/kg	24	–	–
Amoxycillin trihydrate/clavulanate potassium	PO	10–15	12	–	–
Streptomycin sulphate	IM	10	8	–	–
Kanamycin sulphate	IM	10	8	–	–
Gentamicin sulphate	IM	2–4	8	–	12.5
Apramycin sulphate	PO	10–20	12	150	100
Neomycin sulphate	PO	10	8	140	100
Enrofloxacin	IM	2.5–5.0	12	–	–
Trimethoprim/sulphonamide	IM	4/20	12	–	–
Sulphamethazine (10 % oral solution)	PO	50	12	–	80–120
Oxytetracycline hydrochloride	IM	10	12	200–800	–
Oxytetracycline dihydrate (long-acting)	IM	20	48	–	–
Lincomycin hydrochloride	IM	10	12	100–200	30
Tylosin	IM	20–30	12	100	80
Tiamulin	IM	10–15	24	200	60
Virginiamycin	–	–	–	100	–
Bacitracin	–	–	–	250	–
Monensin[a]	–	–	–	100	–

[a]NB: concurrent use of monensin and tiamulin must be avoided, otherwise toxicity will very likely occur.

gastrointestinal tract (systemic availability, 60–90 %) of fasted and fed horses. The addition of an antimicrobial agent to the feed (as a powder) is an unreliable method of dosing horses. Usual dosage regimens for antimicrobial preparations that may be used in horses are presented in Table 9. Parenteral (IV or IM) therapy with conventional (immediate-release) dosage forms is required in the treatment of severe infections. Procaine penicillin G occupies a unique position in the treatment of equine bacterial infections. This long-acting parenteral dosage form (aqueous suspension) of penicillin G provides effective plasma concentrations of the antibiotic for at least 12 h, owing to slow absorption from the intramuscular injection site, and has high activity against commonly isolated equine bacterial pathogens. It is the only long-acting antimicrobial preparation suitable for administration to horses but care must be taken to avoid inadvertent intravenous administration. The intramuscular injection of procaine penicillin G in the neck region (*M. serratus ventralis cervicis*) produces a higher peak plasma concentration and higher systemic availability of penicillin G than injection of the long-acting product at other locations[5] (Fig. 1). The prime site for intramuscular injection in the neck of the horse appears

Table 9: **Usual dosage regimens for antimicrobial preparations used in horses.**

Drug preparation	Route of administration	Dosing rate	
		Dose (mg/kg)	**Interval** (h)
Penicillin G, sodium	IV, IM	15 000 – 30 000 IU/kg	6
Penicillin G, procaine	IM	25 000 IU/kg	12
Ampicillin sodium	IV, IM	10–20	8
Ticarcillin sodium/clavulanate potassium	IV (slowly)	50	8
Cefadroxil	PO	25	8
Cephalexin monohydrate	PO	25	8
Cefazolin sodium	IV	10–20	8
Gentamicin sulphate	IM	2–4	8–12
Amikacin sulphate	IM	4–8	8–12
Trimethoprim/sulphadiazine	PO	5/25	12
Chloramphenicol palmitate	PO	50	8
Chloramphenicol sodium succinate	IV, IM	25	6
Metronidazole	PO	20	12
Oxytetracycline hydrochloride	IV (slowly)	3	12
Rifampin	PO	5	12
Erythromycin estolate	PO	20–25	8(foals)
Ketoconazole	PO	10	12–24

Table 10: **Suggested dosage regimens for antimicrobial preparations that may be used in reptiles[a].**

Drug preparation	Species	Route of administration	Dosing rate	
			Dose (mg/kg)	**Interval** (h)
Ampicillin sodium	Tortoise	IM	50	12
Carbenicillin	Snakes	IM	400	24
	Tortoise	IM	400	48
Gentamicin sulphate	Alligator	IM	1.75	72–96
	Snakes	IM	2.5	72
	Tortoise	IM	2.5	48
Amikacin sulphate	Alligator	IM	2.5	96
	Snakes	IM	5.0	72
	Tortoise	IM	5.0	48
Enrofloxacin	Hermann's tortoise	IM	10.0	24
	Gopher tortoise	IM	5.0	24
Ciprofloxacin	Snakes	PO	2.5	48–72
Trimethoprim/sulphadiazine	All species	IM	5/25	First 2 doses 24 h apart: thereafter 48
Tylosin	All species	IM	10	24
Ketoconazole	Tortoise	PO	15–30	24

[a]Source: Jacobson (1993: adated from Table 29.4)[10].

to be at the level of the 5th cervical vertebra, ventral to the funicular part of the ligamentum nuchae but dorsal to the brachiocephalic muscle[3]. The location of the intramuscular injection site does not affect the bioavailability (refers to rate and extent of absorption) of gentamicin (50 mg/ml solution), nor does gentamicin bioavailability differ following intramuscular or subcutaneous injection[7,20].

Owing to the slow elimination (long half-life) of antimicrobial agents in reptiles, dosage intervals are substantially longer in reptilian compared with mammalian species[10] (Table 10). In order to avoid significantly decreased systemic availability of drugs that are eliminated by renal excretion (*e.g.* beta-lactam and aminoglycoside antibiotics), the site of intramuscular injection should be the anterior half of the body; most reptilian species have a well-developed renal portal system. This also applies to birds.

Fish, in common with reptiles, are poikilothermic (cold-blooded) animals and ambient temperature may have a pronounced influence on the rate of drug elimination, particularly when biotransformation is the principal process of elimination. The half-life of trimethoprim, administered intravenously as trimethoprim/sulphadiazine combination, differs widely between carp (*Cyprinus carpio* L) and mammalian species: carp (40.7 h at 10 °C; 20 h at 24 °C), cattle (1.25 h), horse (3.2 h), dog (4.6 h) and human being (10.6 h). Sulphadiazine half-life similarly differs widely: carp (47 h at 10 °C; 33 h at 24 °C), cattle (2.5 h), horse (3.6 h), dog (5.6 h) and human being (9.9 h). Oxytetracycline is slowly eliminated by glomerular filtration because the drug undergoes enterohepatic circulation. The half-life of oxytetracycline is 89.5 h in rainbow trout (*Salmo gairdneri*) at 12 °C and 80.3 h in African catfish (*Clarias gariepinus*) at 25 °C[8], compared with half-lives in the range 3.4–9.6 h in domestic animals. In fish and reptiles, the elimination of antimicrobial agents increases with increase in ambient temperature. When developing drug products for use in farmed fish (food-producing animals), studies of the relationship between pharmacokinetics of the drugs and ambient (water) temperature should be performed.

Table 11: **Activity of concurrently used antimicrobial drugs.**

Antimicrobial agents	Activity
Combination preparations	
Trimethoprim/sulphonamide	Synergistic: bactericidal against susceptible microorganisms
Ampicillin/sulbactam	Enhanced (broader) activity of the penicillin
Amoxyllin/clavulanate	Enhanced (broader) activity of the penicillin
Ticarcillin/clavulanate	Enhanced (broader) activity of the penicillin
Administered separately	
Ampicillin (or amoxycillin) – gentamicin	May be synergistic, depending on the microorganism
Ticarcillin (or carbenicillin) – gentamicin	Synergistic against some strains of: *Pseudomonas, Proteus, Enterobacter, Klebsiella* spp.
Erythromycin – rifampin	Synergistic; *Rhodococcus equi*
Isoniazid – rifampin	Prevents emergence of resistant strains *Mycobacterium tuberculosis*
Doxycycline – rifampin	*Brucella melitensis* (human beings)
Minocycline – rifampin (or streptomycin)	*Brucella canis* (dogs)
Oxytetracycline – rifampin (or streptomycin)	*Brucella abortus* (horses)
Clindamycin (or metronidazole[a]) – gentamicin	Additive; mixed gram-negative + anaerobic infections
Lincomycin – spectinomycin	Additive; bacterial respiratory infections in cattle

[a]Use metronidazole in horses.

ANTIMICROBIAL COMBINATIONS

The mechanisms of action as well as the susceptibility of microorganisms underlie the type of interaction that may occur (generally additive, but may be synergistic or antagonistic) when antimicrobial agents of different classes are used concurrently (either as combination preparations or administered separately).

Useful combination preparations include trimethoprim/sulphonamide that, through synergistic action, produces a bactericidal effect (at least *in vitro*), amoxycillin/clavulanate and ticarcillin/clavulanate (Table 11). The concurrent use of ampicillin (or amoxycillin) and gentamicin is likely to provide synergistic action at least against streptococci (have a natural permeability barrier to aminoglycosides), while ticarcillin (or carbenicillin) and gentamicin used concurrently act synergistically against some strains of *Pseudomonas, Proteus, Enterobacter* and *Klebsiella* spp. (*i.e.* gram-negative rods). Note that penicillins and gentamicin should not be mixed *in vitro,* since activity of the aminoglycoside would be decreased (owing to chemical interaction). The concurrent use of a bacteriostatic drug and a bactericidal drug, especially a beta-lactam antibiotic, generally results in antagonism. Chloramphenicol and a fluoroquinolone are antagonistic. However, erythromycin and rifampin act synergistically against *Rhodococcus equi,* while tetracycline and rifampin (or streptomycin) used concurrently provide enhanced clinical efficacy against *Brucella* spp. in human beings, horses and dogs. While rifampin is particularly useful against macrophage-associated (intracellular) susceptible microorganisms, it should always be used concurrently with another antimicrobial drug to prevent the rapid emergence of strains resistant to rifampin. In mixed infections with anaerobic involvement, the concurrent use of clindamycin (or, in horses, metronidazole) and gentamicin is the treatment of choice.

Unless specifically indicated, which implies synergistic action and/or the prevention of acquired resistance, or there is circumstantial evidence to support the clinical effectiveness of antimicrobial combinations, the concurrent use of antimicrobial drugs should be avoided. When 2 antimicrobial agents are used concurrently, not as a combination preparation, they must be administered independently at usual dosing rates.

RELATIONSHIP BETWEEN PLASMA CONCENTRATION AND CLINICAL EFFECTIVENESS

Penicillins and cephalosporins act by causing selective inhibition of bacterial cell wall synthesis; they interfere with the final stage of peptidoglycan synthesis. Beta-lactam antibiotics produce a time-dependent bactericidal effect on susceptible bacteria. The overall effectiveness of therapy with penicillins (and cephalosporins) is largely influenced by the aggregate time, though not necessarily continuous, during which effective plasma concentrations (> MIC for pathogenic microorganism) are maintained; peak height determines the rate of penicillin penetration into the site of infection. The clinical effectiveness of discontinuous dosage regimens for penicillins could be attributed to the post-antibiotic sub-MIC effect they exert on gram-positive bacteria. The post-antibiotic sub-MIC effect (PASME) refers to a temporally limited suppression of bacterial growth that occurs at sub-inhibitory concentrations following exposure of susceptible bacteria to drug concentrations above the minimum inhibitory concentration (MIC).

Aminoglycosides inhibit ribosomal protein synthesis in susceptible bacteria by inducing misreading of the genetic code on the messenger RNA template (30S ribosomal subunit). Fluoroquinolones block nucleic acid synthesis in susceptible bacteria by selectively inhibiting DNA gyrase, an intracellular enzyme. Both classes of antimicrobial agent produce a concentration-dependent bactericidal effect.

The clinical effectiveness of aminoglycosides and fluoroquinolones is influenced both by the height of the peak plasma concentration relative to the minimum inhibitory concentration (C_{max}:MIC ratio) and the area under the plasma concentration-time curve that is above the MIC during the dosage interval (AUIC = AUC/MIC). The former is relatively more important for fluoroquinolones; maximum activity is achieved when peak plasma concentration is in the range 5–10 times the MIC. The clinical effectiveness of the aminoglycosides is mainly determined by the area under the inhibitory plasma concentration-time curve (AUIC). The area under the inhibitory concentration curve indicates the degree of exposure of a microorganism to the drug. Aminoglycosides and fluoroquinolones induce a post-antibiotic sub-MIC effect on some species of gram-negative aerobic bacteria. On account of its variable duration, generally from 1–6 h, the post-antibiotic effect is not taken into account when calculating dosage regimens. For the treatment of systemic bacterial infections caused by susceptible microorganisms, the usual

dosage intervals are 8–12 h for aminoglycosides, injected IM or SC, and 12 h for fluoroquinolones (with the exception of marbofloxacin, 24 h), administered orally, in dogs. Some authors contend, from both a safety and clinical efficacy standpoint, that the dosage interval for aminoglycosides could be 24 h[18,21]. Since aminoglycosides are potentially ototoxic and nephrotoxic and can accumulate, due to their prolonged terminal elimination, the monitoring of trough serum/plasma concentrations (C_{min}), which should not be allowed to exceed 2 µg/mℓ, is important particularly in the presence of renal impairment.

It is highly desirable for bactericidal drugs (*e.g.* beta-lactam antibiotics, aminoglycosides, fluoroquinolones) and essential for bacteriostatic drugs (*e.g.* tetracyclines, chloramphenicol and its derivatives, macrolides and lincosamides) to maintain plasma concentrations above the minimum effective concentrations for the duration of therapy. The terms bactericidal and bacteriostatic are relative, not absolute.

DURATION OF THERAPY

Antimicrobial therapy must be maintained for an adequate duration, which is based on monitoring the response both by clinical assessment (resolution of fever, leukocytosis and other signs of inflammation) and bacterial culture. Definitive diagnosis at an early stage of infection and the application of specific therapy, based on knowledge of the causative pathogenic microorganism and its susceptibility, will decrease the overall duration of treatment and minimise residual sequelae. Therapy with an aminoglycoside should not be extended beyond the duration required to treat the infection. The speed of clinical response is generally inversely related to the length of time the infection was present before initiating therapy.

There are certain infections that, owing to the relative inaccessibility of the causative microorganisms to antimicrobial agents, invariably require a prolonged duration (3–5 weeks, rather than 5–8 days) of therapy. They include prostatitis, osteomyelitis and skin infections in dogs, and *Rhodococcus equi* pneumonia in foals (6–16 weeks of age). In the treatment of these infections, preference should be given to the use of orally-effective antimicrobial agents.

VARIABLES THAT INFLUENCE CLINICAL RESPONSE

Even when the antimicrobial drug of choice is administered at the recommended dosing rate, the outcome of therapy is largely governed by the responsiveness of host defense mechanisms. This applies particularly to drugs that produce a bacteriostatic effect. The concentration attained by an antimicrobial agent at the site of infection may be influenced by disease-induced changes in the disposition of the drug as well as by local changes associated with tissue inflammation or abscess formation. Disease states that may alter the disposition of drugs include fever, dehydration, hypoalbuminaemia (associated with chronic liver disease) and uraemia (chronic renal failure). The bactericidal activity of aminoglycosides and fluoroquinolones (apart from difloxacin) against gram-negative aerobic bacteria is greater in an alkaline than in an acidic environment. In the presence of impaired renal function, which may be detected by urinalysis (proteinuria and the presence of casts), dosage regimens for aminoglycosides should be adjusted (preferably by increasing the dosage interval in accordance with the decrease in glomerular filtration rate) in order to avoid drug accumulation with attendant toxic effects (acute tubular necrosis and cochlear damage in dogs or vestibular damage in cats). An indication of the extent of a decrease in the glomerular filtration rate (GFR) may be obtained by measuring endogenous creatinine clearance. In dogs with decreased renal function (GFR < 3 mℓ/min/kg; in normal dogs, GFR = 4.07 ± 0.52 mℓ/min/kg), the reciprocal of serum creatinine concentration provides a clinically useful estimation of the glomerular filtration rate[4] that could serve as a guide for dosage interval adjustment of aminoglycoside antibiotics. The monitoring of trough serum/plasma concentrations of an aminoglycoside is highly desirable in animals with severe infections or renal impairment and is essential in animals with changing renal function.

After an infectious disease has been diagnosed in an animal, the decision has to be made as to whether an antimicrobial agent should be administered. When the answer is positive, and following proper collection of appropriate specimens, the treatment should be promptly initiated with an antimicrobial selected on an informed empirical basis. The microbiological and clinical chemistry results from the samples submitted for analysis, in conjunction with the response of the animal to the initial treatment, provide the requisite information for selecting the antimicrobial agent to use for the continuation of treatment. The usual dosage regimen for the particular antimicrobial preparation selected can generally be applied, while the duration of treatment should be based on monitoring the response both by clinical assessment of the animal and bacterial culture of properly collected specimens. By adopting the approach outlined in this paper, the success of antimicrobial therapy will likely be increased and the indiscriminate use of antimicrobial agents will be reduced. Moreover, the animal owner will become increasingly aware of the fact that there is far more to antimicrobial therapy than the administration of an empirically selected antimicrobial preparation and will ultimately appreciate the longterm benefits and cost-effectiveness of the scientific approach.

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Note added in proof

Foals treated with erythromycin and rifampin for *Rhodococcus equi* infection (pneumonia) could serve as a potential reservoir of *Clostridium difficile* and excrete the microorganism, resistant to both antimicrobial agents, in the faeces. It would appear that erythromycin is the offending drug; it may promote the growth of *C. difficile* in the intestine of the foal, and a variable fraction of the oral dose, seemingly irrespective of the dosage form, is excreted in the faeces (Baverud *et al.* 1998 *Clostridium difficile* associated with acute colitis in mares when their foals are treated with erythromycin and rifampin for *Rhodococcus equi* pneumonia. *Equine Veterinary Journal* 30: 482–488). Coprophagic behaviour of mares housed with erythromycin-treated foals would lead to ingestion of the resistant microorganism and the antibiotic, which could severely disrupt the commensal flora of the large intestine, resulting in acute colitis in the mares. The available evidence suggests that this scenario is nosocomial infection.