8 Antibiotics

Definitions

Antimicrobial drugs = drugs which kill or inhibit the growth and replication of micro-organisms in living tissues.

Antibiotics = naturally synthesised substances secreted by living organisms, usually bacteria or fungi, to inhibit other species. Commercially, some antibiotics are now partially synthesised (ie, the organism is fermented with different substrates to those found in nature to produce different antibiotics) or completely synthesised chemically. These drugs are often called semi-synthetic or synthetic antibiotics. Although this chapter is concerned with antimicrobial antibiotics, other antibiotics are used as anthelmintics and anti-cancer drugs.

Antiseptics = non selective toxic chemicals which are safe enough to be applied to skin to kill micro-organisms, but not safe enough to be given orally or parenterally (see skin pharmacology notes). Just to confuse things, some antibiotics fall into this category, eg, polymixins.

The term antibiotic is used in this chapter to cover all antibacterial drugs given systemically or topically except antiseptics.

Classification of antibiotics

There is an enormous range of antibacterial drugs available. In order to make sensible decisions about their use, it is helpful to divide them up into groups of similar drugs. Antimicrobial drugs can be classified in different ways, each of which is useful clinically for different reasons:

spectrum of activity
bactericidal or bacteriostatic
mechanism of action
chemical family
toxicity

Spectrum of activity

Many antibiotics act at bacterial cell walls or cell membranes. This means that the spectrum of activity often corresponds with Gram staining. This approach to classification is not always applicable, however, since there are organisms which are not easily classified by their Gram staining characteristics.

The antimicrobial drug may have a broad spectrum of activity (i.e. is active against a wide range of different bacteria) or narrow spectrum (i.e. is active against only a few bacteria or one or two families of bacteria). Usually, drugs are classified as broad spectrum if they are active against both Gram positive and Grain negative bacteria.

examples:

broad spectrum - tetracyclines, some cephalosporins, potentiated sulphonamides, fluoroquinolones, some semi-synthetic penicillins e.g. amoxycillin, ampicillin

narrow spectrum, Gram positive - macrolides, lincosamides, older penicillins e.g. benzylpenicillin,

narrow spectrum, Gram negative - aminoglycosides

You must know an antibiotic's spectrum of action in order to treat animals rationally. This is rote learning you just have to do. Bear in mind that as resistance develops, the spectrum will change!

Bactericidal or Bacteriostatic

Bactericidal drugs kill bacteria; bacteriostatic drugs stop them growing and rely on the animal's immune system to get rid of them. However, in reality, the differentiation is not very useful since all you can realistically expect is to influence the competition between the animal and the bacteria in favour of the animal.

Bactericidal drugs can be defined as those for which the reasonably achievable tissue concentration ("break point") is greater than the minimum bactericidal concentration (MBC) for the great majority of susceptible pathogens. They can be (but are not always) bacteriostatic at lower concentrations or against other pathogens.

Bacteriostatic drugs are those for which the minimum inhibitory concentration (MIC) is less than the break point. Nominally, these drugs merely inhibit bacterial cell growth or replication. At very high doses they may be bactericidal. The rational use of bacteriostatic drugs requires the animal to have a competent immune system.

Mechanism of antibacterial action

The main usefulness of knowing the mechanism of action of an antibiotic is that is helps to predict the spectrum of activity and the likelihood of inducing toxicity with many of the drugs. It is of major importance if combinations of drugs are to be used.

Inhibition of cell wall synthesis

To be effective, these drugs require the bacteria to be actively dividing. Therefore, combination with protein synthesis inhibiting drugs tends to antagonise the action of the cell wall synthesis inhibitors.

Because mammalian cells do not synthesise cell walls, these drugs tend to be non-toxic. Bacitracin is an exception to this, and is extremely nephrotoxic. It is only used topically.

eg: penicillins, cephalosporins, vancomycin, bacitracin

Disruption of cell membranes

Since these drugs lead to the rupture of the bacterial cell, they tend to be rapidly bactericidal. They are not dependent

on bacterial replication or growth, and can therefore be combined with other drugs to broaden a spectrum of antimicrobial therapy.

Because mammalian cells have a cell membrane which is similar to that of the bacteria, these drugs tend to have either a narrow therapeutic safety margin, or are too toxic to use other than topically.

eg: polymixin B, colistin, novobiocin, nystatin, amphotericin B

Most antiseptics / disinfectants / detergents also disrupt cell membranes.

Inhibition of protein synthesis

These drugs are selective for bacteria because bacterial ribosomes (where the proteins are made) are different from mammalian ribosomes. Most of these drugs are bacteriostatic.

eg: aminoglycosides, tetracyclines, macrolides, lincomycin, chloramphenicol

Inhibition of DNA synthesis / function

For these drugs their toxicity tends not to be related to their mechanism of action, and varies with each individual drug. Drugs which interfere with mammalian DNA are potentially carcinogenic.

eg: sulphonamides ± trimethoprim, fluoroquinolones, nitrofurans, nitroimidazoles, griseofulvin

Chemical structure

Drugs of the same chemical family usually have the same mechanism of action, so there are only subtle differences between this classification and that of mechanism of action. Classifying drugs by chemical family is most useful to the drug manufacturer and medicinal chemists. This method is marginally useful to clinicians, since bacterial resistance to an antimicrobial drug is often shared with other drugs of the same chemical family.

Toxicity

Nephrotoxicity is common to many antibacterial drugs. Those which cause damage to the renal tubular epithelial cells include aminoglycosides, polymixins, tetracyclines and some of the older cephalosporins. Damage to the collecting ducts and more distal tubular structures can be caused by sulphonamide crystalluria.

Liver damage can be caused by tetracyclines, erythromycin and possibly potentiated sulphonamides.

Aminoglycosides, polymixins and tetracyclines can result in neuromuscular blockade, especially when anaesthetics are present. Of more clinical significance, however, is the ototoxicity of aminoglycosides, which can cause both deafness and/or vestibulocochlear injury. CNS excitement can be associated with the use of procaine salts of penicillins. This is due primarily to the procaine.

Gut problems are commonly caused in the horse and guinea pig by ampicillin, lincomycin and clindamycin upsetting the normal balance of gut flora. This manifests as pseudomembranous colitis or diarrhoea which is potentially fatal.

Bone marrow toxicity is a feature of chloramphenicol, sulphonamide and trimethoprim toxicity. In dogs this results in an anaemia or panleucopaenia which is reversible by withdrawal of therapy.

Drug interactions are a feature of giving antibiotics. Drugs which inhibit hepatic mixed function oxidase enzymes can significantly reduce the elimination of chloramphenicol and tetracyclines, resulting in toxicity. Some diuretics, especially frusemide, significantly increase the chances of inducing nephrotoxicity with aminoglycosides or some obsolete cephalosporins.

Acute hypersensitivity reactions are possible with many antibiotics. Penicillins can cause anaphylaxis, and the horse seems to be a species particularly prone to hypersensitivities, although most reactions to procaine penicillin are probably to the procaine. Care should always be taken with intravenous injections of antibiotics - monitor the animal for potential hypersensitivity reactions.

And finally...

In these notes, the antibiotics have been grouped by their mechanism of action: ie, the bacterial processes with which they interfere.

The use of particular drugs for any given disease in animals is largely empirical rather than being based on good evidence of efficacy and safety. “Commonly used” drugs will change their status according to the latest fashion!

Resistance

Every time an antibiotic is given, there is pressure on the exposed bacterial population to select for resistance. There may be very few resistant bacteria present, but if most of the sensitive ones are killed, the resistant ones can grow to fill the space. Resistance is important, both from the point of view of treating the animal (and contact animals), and from passing resistance on to human pathogens, in either the animal's owner or the general public. Bacterial resistance in people is increasing, probably as a result of poor prescribing practices by GPs, but about half the antibiotics used in NZ are given to animals, so **responsible use of antibiotics by vets is essential**.

Antibiotic resistance is a relative term. It is a situation where a bacterium is not inhibited or killed by concentrations of antibiotic that would normally be lethal to that bacterium. By common usage, resistance relates to antibiotic concentrations achievable in the animal or person being treated for infection. Sometimes the dose can just be increased, but most drugs are too toxic for this.

Bacteria can be resistant because:

the drug does not reach its target, eg

active efflux of macrolides, tetracyclines and streptogramins

the drug is inactivated

ß-lactamase enzymes which inactivate penicillins and cephalosporins

chloramphenicol acetyltransferase acetylates and inactivates the drug

modification of aminoglycosides such as streptomycin and gentamicin

the target is changed

changes to the ribosome which prevent the binding of macrolides such as tylosin and erythromycin

changes to the penicillin binding protein which stops methicillin killing some *Staph aureus*

changes to the bacterial DNA gyrase, preventing the binding of quinolones

Depending on the specificity of the target or efflux mechanism, resistance may be to a single drug or a whole class, or classes of drug.

Antibiotic resistance in bacteria may be intrinsic or acquired. **Intrinsic resistance** occurs when a bacterium normally does not possess the particular target structure of the antibiotic, or does not possess the sort of cell wall which allows the drug in. Examples include the resistance of Gram negative organisms to penicillin. **Acquired resistance** occurs when a bacterial strain that is normally susceptible becomes resistant. A single bacterial strain will often be resistant to several different antibiotics via different mechanisms of resistance. These may be acquired either in single or multiple steps.

Bacteria can acquire resistance by mutation of their own DNA or, more importantly, by acquiring some DNA from another bacterium.

Chromosomal mutation

Mutation occurs all the time, and most mutations are of no use or detrimental to the bacterium. This type of resistance tends to develop slowly in small steps, but there are exceptions. The importance varies with different antibiotics - most important for streptomycin, erythromycin and rifampicin. This type of resistance is probably favoured by intermittent use of low doses of antibiotic.

Transferable drug resistance

Bacteria share DNA readily, both within and across species, including non-pathogenic species. This may occur by several different processes:

Conjugation is probably most important. A donor bacterium conjugates with a recipient and passes across DNA, including plasmids, which may contain resistance genes. This may occur between species, mainly in Gram - bacteria and enterococci. The plasmids may carry genes for resistance to a single or many antibiotics. The composition of plasmids is continually being changed by the insertion of transposons, many of which carry antibiotic resistance genes.

DNA can also be transferred by **transduction**, where a bacteriophage takes DNA from one bacterium and puts it into another. This seems particularly important in *Staph aureus* where plasmids carrying resistance genes for penicillins, erythromycin, tetracyclines or chloramphenicol can be transferred. It is also important in *Streps* for the transfer of genes for toxins.

The simplest method, **transformation**, is where bacteria pick up free DNA lying around. The importance of this is unknown, but it is certainly possible in the gut. It probably only occurs with Gram positive bacteria. Sources of free DNA could include dead bacteria, either gut inhabitants or the bacteria used to produce growth promoters, which are present in the crude extracts used for this purpose. (These bacteria must, by definition, be resistant to the antibiotic they produce.) Less importantly (?), many transgenic crops used for animal feed overseas (soya beans and maize) contain antibiotic (usually ampicillin) resistance marker genes.

For an animation of these processes, look at `http://www.fda.gov/cvm/antimicrobial/antiresistvideo.htm` Beware - it is a ridiculously large file size!

Resistance is usually only measured in pathogens, but commensals can act as a reservoir of resistance genes. The importance of this is unknown but is likely to be large. Giving antibiotics selects for resistance among commensals too! This has been highlighted by the development of multi-resistant ubiquitous bacteria such as enterococci, which, although not normally regarded as pathogenic, can kill severely immunocompromised patients in intensive care units in hospitals.

Reducing resistance

Control of resistance depends on responsible use (see

later), but is mainly a matter of common sense and only using antibiotics where absolutely necessary. Relying on new drugs coming along is not an option - bacteria move much faster than the drug companies or regulators. Most human hospitals have a policy of reserving some antibiotics (eg, fluoroquinolones, glycopeptides and modern cephalosporins) for life threatening diseases, to prevent the development of resistance to them. This should happen in veterinary practice too.

Problem bacteria in people

There are several areas of concern about resistance in human medicine, many of which are relevant to us. Increasingly, plasmids, or other transmissible bits of DNA encoding resistance, are at least as important as species of bacteria since movement between species seems to be common.

Food poisoning caused by resistant Gram negative bacteria (*E coli* O157, *Salmonella* Typhimurium, especially DT104, and *Campylobacter* spp.) are probably zoonoses in many cases and are common overseas. In the UK, 4.7% of cattle and 1.7% of sheep carry *E. coli* O157 (no figures for NZ, but almost certainly not as high as the UK). Antibiotic resistant campylobacter are common in NZ, most of the others are probably rare imports. Extended spectrum ß-lactamase (ESBL) producing *E. coli* (ie, resistant to cephalosporins) are starting to cause concern here.

Gram positive pathogens, particularly methicillin resistant *Staph aureus* (MRSA) and vancomycin resistant enterococci (VRE), can be virtually untreatable. It is possible that resistant enterococci from animals pass on resistance genes to human enterococci which pass them on to MRSA. This has been shown *in vitro*, but not (yet) *in vivo*. Vancomycin intermediate *Staph aureus* (VISA) is becoming a problem in Japan and Europe. It is very bad news. Low level MRSA is fairly common in Pacific Islanders, but high level MRSA (epidemic MRSA type 15 (EMRSA-15), imported from the UK) is also increasing in NZ, comprising 7% of *Staph. aureus* isolates in 2001 (up from 4% in 2000) (cf UK - almost 50% in 2001). This particularly nasty bug has been traced back to a patient with eczema in Guildford (near London) in 1960. It has since spread around the world, mutating as it goes and acquiring extra resistance genes. There are no figures for NZ, but MRSA kills 5,000 people a year in the UK, and is involved in the deaths of 15,000 more. MRSA was reported from a dog in Auckland in 2005.

Drugs used for *Staph aureus* in people:

penicillin - practically useless now because of resistance (ß-lactamases)

flucloxacillin - related to methicillin and so no use against MRSA

rifampicin - resistance develops quickly and this drug is usually reserved for TB

vancomycin - main MRSA drug

linezolid - second line MRSA drug

quinupristin & dalfopristin combination - recently approved for use in NZ, drug of last resort for named patients in hospitals

Vancomycin intermediate *Staph aureus* (VISA) has been around in Japan and the USA for several years, but in July 2002 the first fully vancomycin resistant *Staph aureus* was reported from the USA. Luckily for the patient, it was not resistant to chloramphenicol.

VRE was isolated from five people in NZ in 2001; one patient and four carriers. The patient died. There were 10 reports in 2002, but no details yet. It has also been isolated from chickens in Otago (it has not been looked for anywhere else in the country). Only two strains are involved in both people and poultry.

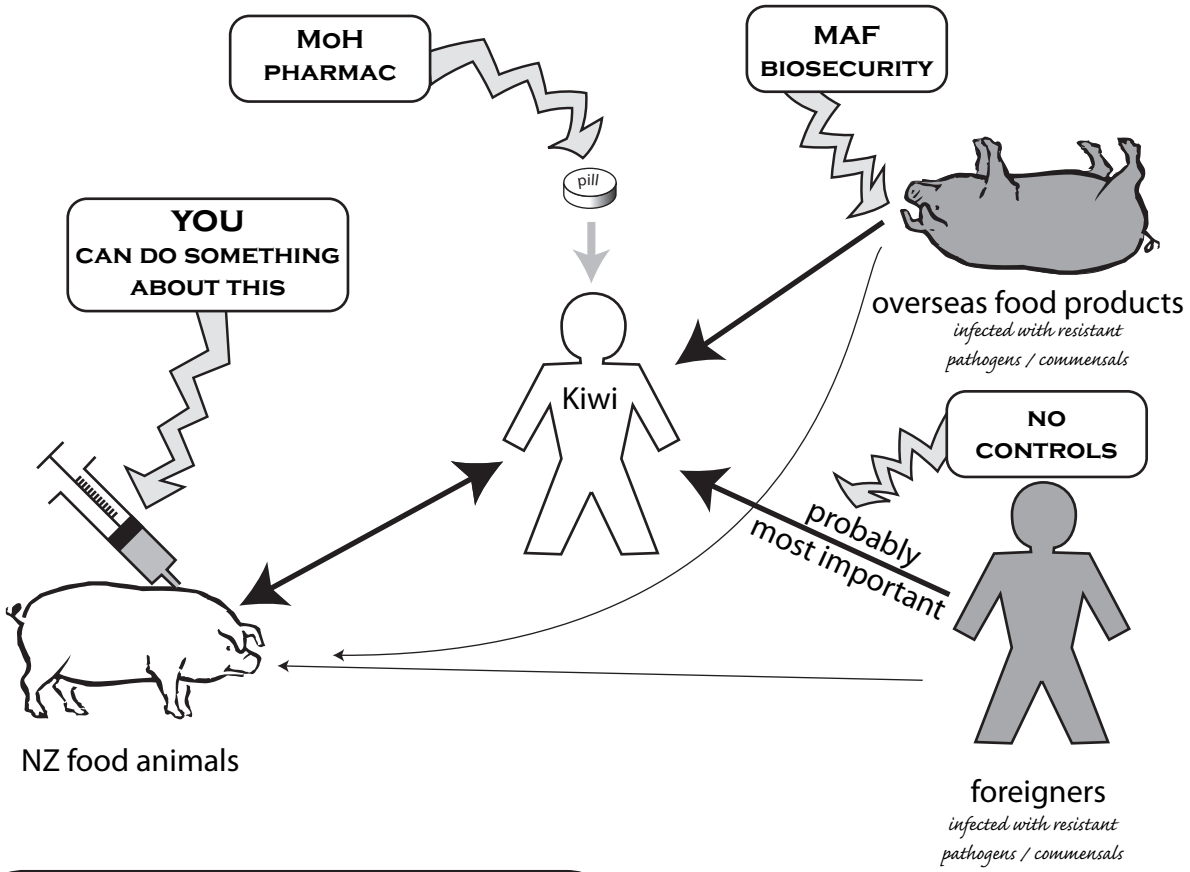
Multiple drug resistant *Shigella dysenteriae* is a big problem in developing countries, but does not receive much attention elsewhere. Resistance probably arises from inappropriate human treatment, but can spread indirectly from animals.

Acinetobacter used to be a commensal found in hot, dry countries. It has recently become established in hospitals in temperate climates. The current theory is that it was brought in in contaminated wounds in soldiers serving in Iraq and Afghanistan, but it has not been studied much in animals.

Drug resistance in pneumococci and *Mycobacterium*

group	description	examples
A	Essential antibiotics used in human medicine where there are few or no alternatives for many infections	anti-pseudomonal penicillins, 3rd & 4th generation cephalosporins, carbapenems, monobactams, some aminoglycosides, some macrolides, glycopeptides, nitroimidazoles, fluoroquinolones, streptogramins, antimycobacterials
B	Antibiotics used in people for which there are alternatives but fewer than group C; or there are concerns that use will lead to increased resistance to group A drugs	ß-lactamase inhibitors, anti-staphylococcal penicillins, 1st and 2nd generation cephalosporins, certain aminoglycosides, certain macrolides, lincosamides, non-fluorinated quinolones, chloramphenicol
C	Antibiotics used in human medicine for which there are a reasonable number of alternative agents available in different classes to treat most infections	benzylpenicillin, certain aminoglycosides, tetracyclines, sulphonamide-trimethoprim combinations, certain macrolides, polypeptides
D	Antibiotics with no equivalents in human medicine	ionophores / polyethers

Australian classification of antibiotics - use drugs from as low a group as possible.



Possible sources of antibiotic resistant bacteria in NZ.

The killer bug and how it has developed
(Daily Telegraph 27/08/2001)

1944
Penicillin, the first antibiotic, is introduced, and proves devastatingly effective against Staphylococcus aureus.

1945
Doctors notice that some Staphylococcus aureus infections are not being killed off by penicillin.

1945-55
New antibiotics, derivatives of penicillin, are introduced.

1955
A strain of Staphylococcus aureus (MSSA) has become immune to penicillin, streptomycin, tetracyclin and erythromycin.

1955-60
An epidemic gathers pace of Staphylococcus aureus infections which resist antibiotic treatment.

1960
Methicillin invented in England by the Beecham company and is effective against the resistant strain of Staphylococcus aureus. The epidemic declines.

1961
The first Staphylococcus aureus bacterium with immunity to methicillin (MRSA) emerges in Guildford, Surrey. It is a direct descendant of the 1955 strain, but has now acquired an extra piece of DNA - the mecA gene - which makes it methicillin-resistant. A new outbreak of MRSA infections begins in the UK, and spreads to Scandinavia and the Mediterranean. In 1975 the epidemic starts to die back.

1980
A new epidemic of MRSA starts, and spreads to the US. After several years it dies back.

1986
A strain of MRSA is DNA fingerprinted in Barcelona and named "The Iberian Clone". It is another direct descendant of the 1960 strain.

1990
A third epidemic of MRSA starts, and spreads to the Far East. MRSA is now a worldwide threat.

1995-2000
Doctors report the first cases of MRSA which are also resistant to vancomycin. These, too, are descendants of the 1960 strain.

tuberculosis is also a problem, but no way has been found for blaming this on the veterinary profession yet. Multiple drug resistant (MDR) TB is an increasing problem worldwide. The next stage up, extensively drug resistant (XDR) TB has not reached NZ yet, but it is probably only a matter of time. This is resistant to just about everything. Its emergence has been attributed to using second line drugs to treat uncomplicated TB - some of the drugs used for TB in people can also be used for other things in animals: **they should be avoided or used with extreme care**. They may include:

rifampicin - sometimes used in animals

clarithromycin / azithromycin - sometimes used in animals

ethambutol, isoniazid and ***pyrazinamide*** - not used in animals

streptomycin (only used as a last resort) - commonly misused in animals

New generation ***fluoroquinolones*** and ***linezolid*** have been used and may become more popular.

Multidrug resistant TB is still rare in NZ, but is killing huge numbers of people overseas. It is practically untreatable.

The WHO calculates that 30% of the world population carries TB, so this is likely to become a more important issue in the future.

Problem bacteria in animals

Pseudomonas aeruginosa is generally regarded as an environmental organism which is an opportunistic pathogen of

animals and people. It has a much larger genome than other bacteria, which means that it has lots of redundant systems it can use if one is knocked out by an antibiotic (eg, it has 12 drug efflux pump systems). In practical terms, resistance will develop rapidly, often over the course of treatment. Non-antibiotic treatments are best where possible - for instance, it does not like acid conditions and dilute vinegar can often stop it growing in dogs' ears. Transfer of antibiotic resistant *Pseudomonas* from animals to people has not yet been shown, but is a real possibility.

Pseudomonas (and some other bacteria) can sense when there are others around, and when a quorum forms, they cooperate to produce a slimy biofilm which is resistant to most chemicals. This can be very bad news, and cannot be prevented at present.

Food for thought?

Although tranfer of resistance from animals to people is usually blamed on the use of growth promoters in food animals, no one has looked closely at companion animals yet. There is one reported case of multiresistant *Salmonella* Typhimurium transfer from a dog to its owner, but it probably occurs commonly. Several recent studies have shown that a large proportion of pets and their owners have the same strains of bacteria in their gut. Development of resistant bacteria after treatment is relatively common in dogs and cats, and most owners do not practise any sort of infection control. Beware!

Situation in NZ

Antibiotic resistance in bacteria important in animals is not recorded in any systematic way, although this is starting to change as ESR collate records from people and animals. Anecdotal evidence suggests that we do not have the large scale problems seen overseas (14,000 people/year die in the USA from multiple drug resistant infections). Let's keep NZ free of them.

The law is in the process of changing to make it more difficult for vets to use valuable antibiotics indiscriminately (see law notes).

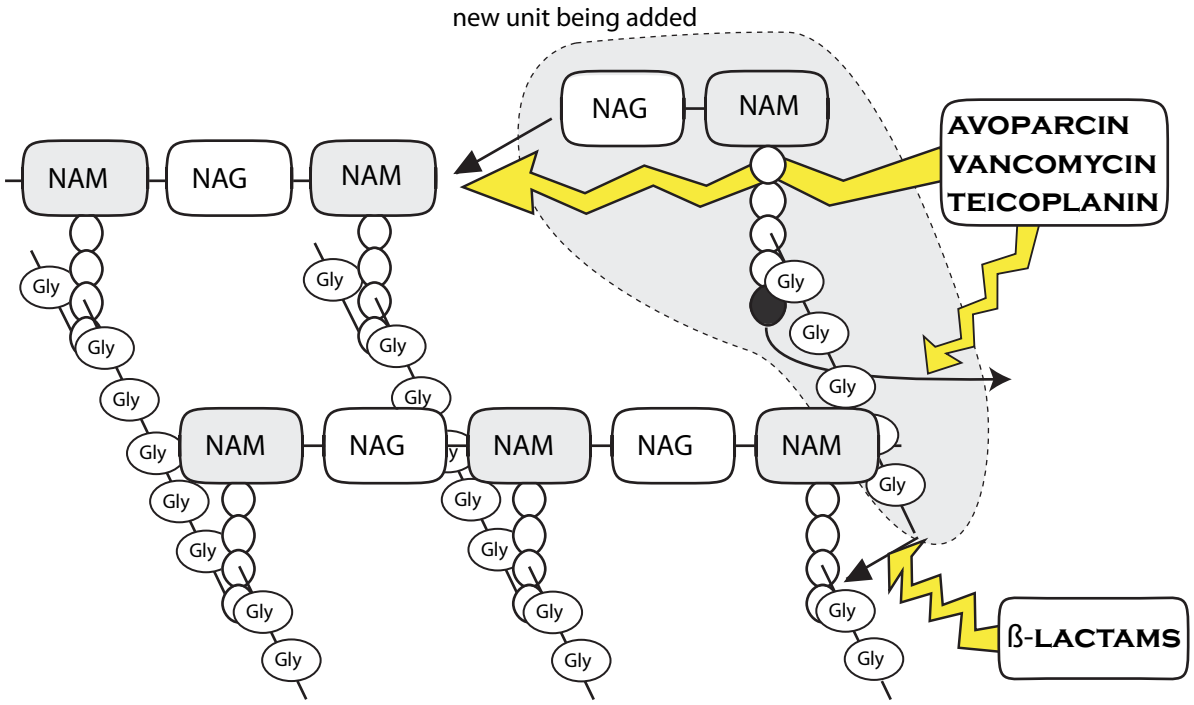
Antivirals and antifungals

Resistance to these can occur as well, and is starting to emerge as a problem in people. Amantadine fed to chickens in China to prevent bird 'flu' has resulted in widespread resistance.

Reducing resistance

- Wash your hands / gumboots!
- Isolate the patient.
- Use antiseptics / disinfectants where possible.
- Choose a drug on resistance testing, where practicable.
- Use narrow spectrum antimicrobials whenever possible.
- Use the full effective dose for as short a period as possible.
- Use antibacterials not prone to producing resistance.
- Restrict the prophylactic use of antimicrobials to high risk patients only.
- In chronic care patients, regularly (but not frequently) change antimicrobial drugs.
- With aminoglycosides, use the longest effective dosage interval.

Cell wall synthesis



Bacterial cell wall synthesis. NAM and NAG - saccharide chains with peptide dangly bits. These are connected by cross links of five glycines.

Penicillins

Penicillins were the first antibiotics in clinical use (1942) and are still going strong. **Benzylpenicillin** (penicillin G) and its orally active analogue **phenoxymethyl penicillin** (penicillin V) are still used, although a wide range of semi synthetic penicillins are also on the market, eg, **ampicillin, amoxycillin, cloxacillin**, etc, etc.

Mechanism of action

Inhibition of bacterial cell wall synthesis. The final step in peptidoglycan synthesis in the bacterial cell wall is the transpeptidation step (see diagram). This reaction is catalysed by bacterial cell wall enzymes which differ from bacteria to bacteria and are collectively called the penicillin binding proteins. Penicillins bind covalently to these.

Failure to complete the synthesis of peptidoglycan results in weak points and holes in the cell wall of the replicating bacteria. Osmotic pressure forces the cell membrane through the holes and it ruptures.

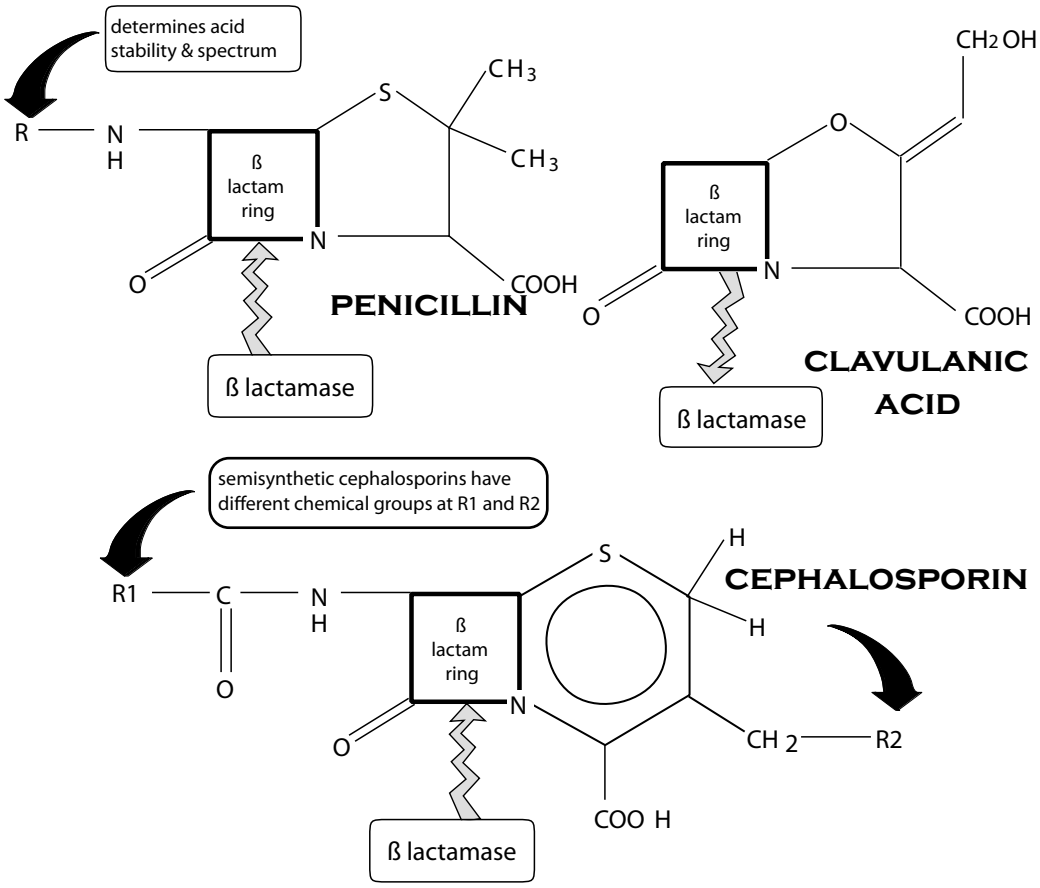
Spectrum of activity

Naturally occurring penicillins (e.g. benzylpenicillin) are primarily active against Gram positive bacteria. Gram negatives are protected by their outer cell membrane.

Semi synthetic penicillins fall into several groups. Some are acid resistant and are therefore active when given orally, e.g. phenoxymethyl penicillin (penicillin V) and many of the broader spectrum semi-synthetic drugs. Some penicillins also kill Gram negative bacteria, e.g. ampicillin, hetacillin (an ampicillin pro-drug), amoxycillin, cyclacillin, pivampicillin, carbenicillin, ticarcillin, piperacillin, mezlocillin, azlocillin. Some are ß-lactamase (penicillinase) resistant, and therefore have more activity against ß-lactamase producing bacteria, e.g. oxacillin, cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin. Some are useful against *Pseudomonas* spp, eg, ticarcillin and pipercillin.

Resistance

Many bacteria produce ß-lactamase, which breaks open the ß-lactam ring and inactivates the penicillin. Gram



The structure of penicillins. Many bacteria are resistant because they produce β *lactamase. The six sided ring on cephalosporins protects the* β *lactam ring to a large extent. Clavulanic acid binds to and inactivates the* β *lactamase.*

positive organisms (especially *Staph aureus*) secrete their ß-lactamase into the intercellular fluid, where it can diffuse away. The gene for ß-lactamase is usually on a plasmid. Most Gram negative bacteria are inherently resistant because of low permeability, lack of penicillin binding protein, and a wide variety of chromosomally derived ß-lactamases in the periplasmic space. Plasmid derived ß-lactamases are also common in Gram negative bacteria. Different ß-lactamases (and there are lots of them) are effective against different ß-lactam drugs.

One way around this problem is to use drugs with broad spectrum ß-lactamase inhibiting effects (but no antibiotic effects) such as clavulanic acid, sulbactam and tazobactam in combination with penicillins. Because of the location of the ß-lactamases, the antagonism of Gram negative ß-lactamase is not as reliable as it is for Gram positive ß-lactamase producing bacteria.

Another way around the problem is to make the antibiotic resistant to ß-lactamases. This resistance is not absolute - there are hundreds of different sorts of ß-lactamase. The ß-lactamase resistant penicillins tend to remain susceptible to ß-lactamases of some Gram negative bacteria, and most *Bacteroides* spp. Extended spectrum ß-lactamases producing bacteria have been isolated in people in NZ - these destroy most ß-lactam drugs but are thankfully rare - at the moment.

For more on ß-lactamases, see: `http://bmj.bmjjournals.com/cgi/content/full/327/7425/1209`

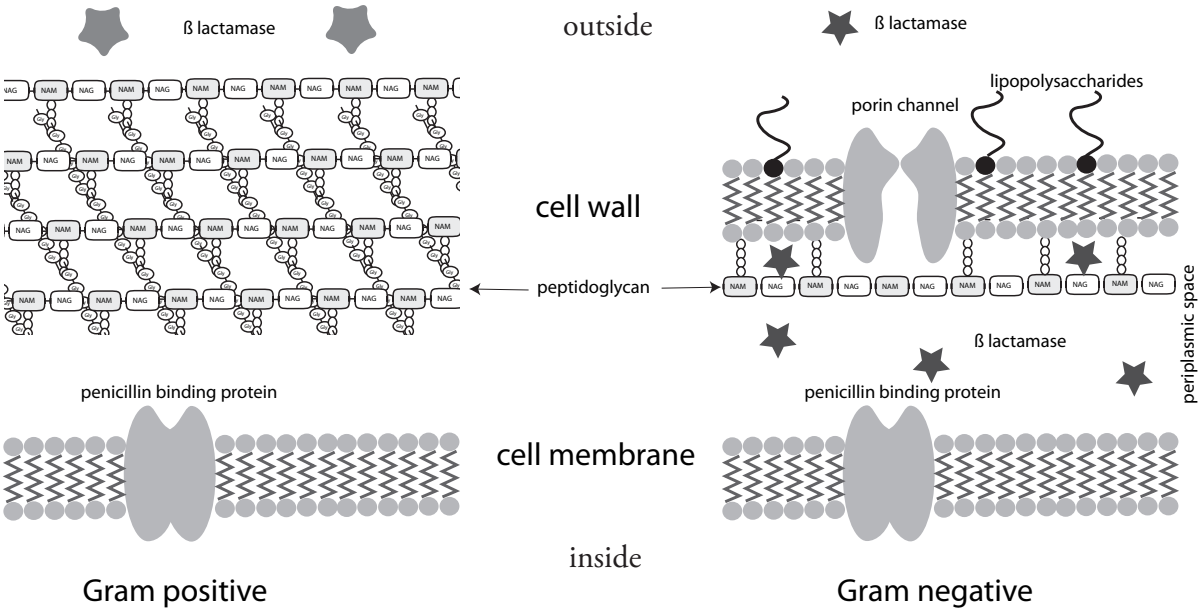
Streps sometimes develop resistance to penicillins by changing their penicillin binding proteins. This has been shown with *Strep pneumoniae* in man, and may be the cause of increased resistance in *Strep uberis* in cows.

MRSA have a gene, *mec-A*, which codes for a different penicillin binding protein, PBP2A. This can take over if the normal PBP is knocked out by ß-lactams, so MRSA are resistant to most ß-lactams.

Toxicity

Allergic reactions are the most common form of toxicity, particularly in horses (and people). Guinea pigs and hamsters are also sensitive to penicillins either through allergies or alterations to intestinal flora: do not use penicillins in these species.

When given intrathecally to patients with meningitis, penicillins have caused convulsions, possibly due to the procaine salts used. Procaine is also incriminated as the cause of CNS excitation and collapse in horses given procaine penicillin. This may be the result of inadvertent intravenous administration of these intramuscular preparations, but is



Different structures of G+ and G- bacterial cell walls. β-lactamases are trapped in the periplasmic space in G- bacteria where they reach a higher concentration than the equivalent enzymes secreted by G+ bacteria.

more likely an immune mediated problem. Some brands or batches have high concentrations of free procaine, which may be absorbed rapidly from intramuscular sites.

Pharmacokinetics

Most penicillins are weak organic acids with a pKa of about 2.7. Therefore they are ionised at blood pH and are confined to the extracellular fluid. They do not cross lipid membranes well and therefore penetrate some body compartments poorly, eg eye, cerebrospinal fluid, prostate. However, in inflammation the lipid barriers are often disrupted and penicillins can be clinically useful. Esters such as **penethamate**, which act as produgs, are used because they cross membranes much more easily.

Penicillins are hydrolysed by strong acids and deactivated in the stomach. Some semi-synthetic penicillins have bulky side chains which sterically protect against this effect and are therefore useful when given enterally eg phenoxymethyl penicillin, ampicillin and amoxycillin.

Most penicillins are substrates for the organic anion transporters of the renal proximal tubule epithelial cells and of the choroid brush border membrane. This means that they are actively secreted into the urine and actively removed from the cerebrospinal fluid. Secretion is the most important mechanism for elimination from the body for many of the penicillins. Some semi synthetic penicillins are metabolised, and others (eg amoxycillin) are also concentrated in the bile sufficiently to achieve therapeutic concentration in the bile ducts and small intestine.

Other weak acids, such as aspirin and probenecid, compete for the organic anion transporters, and therefore co-administration with penicillins results in a decrease in the clearance, or an increase in the half-life of the penicillins. This has been exploited clinically in people but is not well characterised for domestic animals.

Pharmaceutical considerations

The duration of action of intramuscular preparations of benzylpenicillin can be altered by using salts of varying solubility:

- Na or K salts = 4 to 6 hours
- aqueous procaine salt = 24 hours
- procaine salt in oil = 48 hours
- benzathine salt = several days

The more slowly absorbed salts result in lower peak plasma levels, and if inadequately dosed will result in subtherapeutic plasma or tissue concentrations. There is now evidence that benethamine and benzathine salts of penicillin when used alone never result in plasma concentrations of penicillin which are likely to be effective.

Sodium and potassium salts of penicillin can be given intravenously, but care should be taken not to give a toxic dose of potassium. Rapid boluses will transiently depress cardiac output, presumably because of the low pH.

Penicillins will precipitate when mixed *in vitro* (i.e. in a bottle or syringe) with basic drugs, such as aminoglycosides. This can cause confusion because *in vivo* penicillins and aminoglycosides can be synergistic under some conditions. They should be administered separately unless they come as a mixture.

Drugs

Benzylpenicillin (penicillin G) is effective against most Gram positive bacteria except those producing ß-lactamase (mainly *Staphs*). Parenteral only: sodium and potassium salts are usually given iv, others im or sc. Frequently misused as a prophylactic antibiotic in surgery. Frequently used in combination with aminoglycosides in septicaemia, and other severe infections. Quite potent against anaerobes in addition to susceptible Gram positive bacteria. Cheap. 1 international unit (IU) = 0.6 µg Na benzylpenicillin. Phenoxymethyl penicillin (penicillin V)is very similar but can be given orally. It is underused in veterinary practice.

Cloxacillin is active against Gram positive bacteria only, including many ß-lactamase producers. Frequently used as an intramammary preparation for treatment and prevention of *Staph. aureus* mastitis in dairy cattle. Also formulated as a ointment for ophthalmic use. **Flucloxacillin** is very similar (but has better bioavailability after oral administration) and is used in people for *Staph* infections.

Ampicillin is broad spectrum and widely used orally or parenterally. Trihydrate salts for im or sc injection tend to clog needles finer than 20SWG, and tend to sting. Low toxicity. Absorption after oral administration is markedly impeded by food.

Amoxycillin (amoxicillin INN) is very similar to ampicillin. Broad spectrum. Superior in that food tends not to effect its oral absorption as much. Trihydrate salt does not clog syringes but does sting (a little) when administered sc (and presumably im).

Co-amoxyclav (amoxycillin and clavulanic acid) (Clavulox, Clavamox, Augmentin, Synulox, etc) is a combination frequently over-used in small animal medicine. It is broad spectrum and ß-lactamase resistant. Should be reserved for cases with known ß-lactamase producing bacterial infections, or for empirical therapy where these bacteria are very likely, eg skin.

Carbenicillin (obsolescent and not available in NZ), **ticarcillin** (± clavulanic acid) and **piperacillin** (± tazobactam) should be reserved for treating *Pseudomonas* and *Proteus* infections. They are parenteral only and have a very rapid clearance (short half life). Since *Pseudomonas* infections are usually iatrogenic, there should be no reason to use these in normal practice.

Use

Benzylpenicillin is the drug of choice for most Gram positive infections and is widely used in all species, except small mammals in which it can cause a fatal enterocolitis. Where there is likely to be a mixed infection, ampicillin or amoxycillin (± clavulanic acid) are often used. Cloxacillin is very widely used to treat or prevent *Staph aureus* mastitis in cows, since the *Staphs* often produce ß-lactamase.

Human use

Co-amoxyclav is the most widely used broad spectrum antibiotic by a long way, but all the penicillins are extensively used. Resistant *Strep pneumoniae* can be a problem, as can allergic reactions to penicillins as a group (macrolides are usually used instead).

commonly used drugs

penicillin G
ampicillin
amoxycillin
co-amoxyclav
cloxacillin (intramammary)

Cephalosporins

Cephalosporins are also ß-lactams. They should be reserved for cases where culture and sensitivity indicates that they are the most appropriate choice. The use of cephalosporins in empirical therapy cannot be justified (but is often done in practice).

Names

Cephalosporins discovered before 1974 have traditionally been spelt with a ph, while more recent drugs use an f. The current INNs all use an f and incorporate other spelling changes as well such as t instead of th. To reduce confusion, names here are BAN / USAN.

Mechanism of action

Same as penicillins.

Spectrum of activity

There are many different cephalosporins (certainly far too many to memorise their names). They can be roughly divided into three broad groups (generations) but this classification breaks down with the newer drugs. For instance, the commonly used veterinary drug ceftiofur is technically a third generation cephalosporin but is clinically identical to a typical second generation cephalosporin.

First generation (or natural) cephalosporins are broader in spectrum than penicillins, somewhat comparable to ampicillin. They tend to be effective against ß-lactamase producing *Staphylococci*. eg cephalexin, cephalothin

Second generation cephalosporins are more effective for Gram negative organisms, but retain their Gram positive activity, although slightly reduced in comparison to first generation. They are frequently active against anaerobic bacteria. eg cefuroxime

Third generation cephalosporins have predominantly Gram negative activity, and also have reasonable activity against anaerobic bacteria. eg cefotaxime

There are also several drugs classified as fourth generation.

More rational ways of classifying cephalosporins on spectrum of activity have been proposed. The Williams system is most commonly used, and the USP uses a modified version of this. All these classification systems are of dubious value with modern drugs - each drug is different.

Resistance

Mainly by extended spectrum β–lactamases, either inherent or chromosomally transmitted (particularly *Pseudomonas,* and more recently, coliforms). Plasmid mediated resistance can also occur. Reduced membrane permeability is probably less important, although this can produce cross resistance with other classes of antibiotic.

Bacteria generally resistant to cephalosporins include: MRSA and coagulase negative staphs, *Enterococcus*, *Listeria*, *Clostridium difficile*, atypical *Pseudomonas* spp and *Campylobacter* spp.

Third and fourth generation cephalosporins should be reserved for serious infections in people, and **not used in animals**. Ceftiofur is technically a 3rd generation drug but behaves more like a 2nd generation caphalosporin; even so, it is overused. Although it is registered for foot rot in cattle, this

generation	spectrum	veterinary drugs	human drugs
1 oral	good G+, moderate G-, not *Pseudomonas*	cephalexin, cefadroxil	cephalexin, cefadroxil, cephradine
1 parenteral	very good G+, moderate G-, not *Pseudomonas*	cephalothin, cephaloridine, cefapirin, cephalonium	cephazolin, cephradine
2 oral	fair G+, good G-, not *Ps*		cefaclor
2 parenteral	fair G+, good G-, not *Ps*	cefuroxime	cefuroxime, cephamandole
3	moderate G+, very good G-, some activity against *Ps* and *Bacteroides*	ceftiofur cefovecin	cefotaxime
3 antipseudomonal	moderate G+, very good G-, good *Ps*		ceftazidime, cefoperazone, ceftriaxone
4	very good G+, very good G-, good *Ps, Bacteroides, E. faecalis*	cefquinome	cefpirome, cefepime
cephamycins	moderate G+, good G-, not *Ps*, good *Bacteroides*		latamoxef, cefotetan, cefoxitin

There are lots of cephalosporins - these are the ones available in NZ at the moment or likely to get here soon. The spectra of activity are broad generalisations, there are big differences between drugs!

Williams classification

group		spectrum	drugs
oral		good G+, moderate G-, not *Pseudomonas*	cephalexin, cefadroxil, cefaclor
parenteral	1	very good G+, moderate G-, not *Pseudomonas*	cephalothin, cephazolin cephaloridine, cefapirin
	2	fair G+, good G-, not *Pseudomonas*	ceftiofur, cefuroxime, cephamandole
	3	good *Pseudomonas*	ceftazidime, cefoperazone, ceftriaxone
cephamycins	4	moderate G+, good G-, not *Ps*, good *Bacteroides*	latamoxef, cefoxitin

The Williams classification - occasionally used instead of the generation system. It also falls down over differences in the drugs.

use is highly irresponsible. Second generation drugs should only be used for serious infections where nothing else is likely to work. Induction of extended spectrum ß-lactamases by the indiscriminate use of generation 1 or 2 cephalosporins can confer resistance to generation 3 or 4 cephalosporins.

Toxicity

Allergic reactions occur, similarly to penicillins. Local tissue reactions at the site of injection also occur. Cephalosporins can lead to the development of a positive Coombs test (humans).

Some older cephalosporins caused kidney failure, particularly in combination with frusemide. These have now been withdrawn.

Prolonged therapy with some third generation cephalosporins can cause blood clotting disorders through inhibition of vitamin K metabolism (very rare).

Super-infections of the gastrointestinal tract have been reported.

Pharmacokinetics

There are big differences between individual drugs which influence their clinical use. Cephalosporins for parenteral use are poorly absorbed orally, but those prepared for oral administration are almost completely absorbed. Hepatic biotransformation occurs with some of these drugs and is usually deacetylation to active metabolites.

Most cephalosporins are excreted unchanged by the kidney (60 - 100%). The major exception is cefoperazone, which is 80% excreted in the bile. Most cephalosporins are secreted by the organic anion transporters, and therefore probenecid or aspirin inhibits their renal secretion, similarly to penicillins. However, cephaloridine, ceftazidime and ceftriaxone are almost 100% filtered, with negligible secretion.

In general, cephalosporins (particularly the newer ones) have short half lives in domestic animals (although they have been designed to have long half lives in people), and therefore should be dosed at least 8 to 12 hourly. In contrast, ceftiofur, licensed for use in cattle, has an active metabolite with a long half life, and therefore can be dosed every 24 hours. Note that this long dose interval is only appropriate for ceftiofur when being used for bovine respiratory diseases caused by *Pasteurella* spp, since they are extremely sensitive to ceftiofur. If using the drug off label, for other bacterial infections or in other species, some consideration should be given to increasing the dose frequency, possibly to every 12 hours or less. Ceftiofur is sometimes used in dairy cows as it has a zero milk withholding time. (It does not get into the milk at doses suitable for *Pasteurella*.)

Cefovecin has an exteremely long half life in dogs and cats because it is very highly protein bound. It maintains therapeutic concentrations for about two weeks, then subtherapeutic concentrations for about a month. This seems like an ideal way to induce resistance.

Use

Cephalosporins are grossly overused and abused in veterinary practice. A variety of oral cephalosporins are sold as broad spectrum antibiotics for small animals; ampicillin would work as well in most cases, or co-amoxyclav for the penicillinase producers. Several first generation cephalosporins are sold for intramammary use in cows with mastitis. This use is easier to justify, as *Staph. aureus* is often resistant to penicillin, but cephalosporins are no better than cloxacillin. Clinical "resistance" in *Staph. aureus* is usually caused by drugs failing to get to the bacteria, cephalosporins are no better than penicillins in this respect.

Ceftiofur is licensed to treat foot rot in cattle (not a sensible use of a valuable drug) as well as respiratory disease in cattle, pigs and horses. The cattle dose is based on treating *Pasteurella* pneumonia (rare in NZ) and is very low for other infections, ie, likely to induce resistance. It has a nil milk withholding time because it does not get into milk - do not use it for mastitis!

Human use

Third and fourth generation cephalosporins are reserved for life threatening infections. They are only used in hospitals after approval from an infectious diseases specialist and are not used lightly. First generation drugs are used in the same way as in veterinary practice, but attempts are being made to reduce this use to avoid selecting for extended spectrum ß-lactamase producers. These are currently causing problems in Hawke's Bay and Auckland (and in dogs in several Australian vet schools).

Abuse of third and fourth generation cephalosporins by vets could easily result in regulation to reserve these drugs for people - beware!!!

commonly used drugs

far too many!

Carbapenems & monobactams

These drugs were developed to deal with ß-lactamase producing bacteria. Some bacteria, particularly *Staphs* and *Pseudomonas* have evolved to cope with them.

Imipenem is a carbapenem (always combined with cilastin, which inhibits metabolism in the kidney). **Meropenem** is similar. They are active against most bacteria, including *Pseudomonas* and anaerobes. They are always given iv and should be reserved for serious infections caused by multiply resistant Gram negative bacteria in people. They are the last resort for ESBL producing coliforms. **Do not use in animals**.

Aztreonam is a monobactam (ie it only has a ß-lactam ring). It is only active against Gram negative aerobes (may be synergistic with aminoglycosides), particularly *Pseudomonas*. It is inactivated by extended spectrum ß-lactamases. It has a short half life, but penetrates the CNS well. Very expensive. **Do not use in animals**.

Glycopeptides

Vancomycin is a glycopeptide with seven amino acids isolated from *Amycolatopsis* (*Nocardia* / *Streptomyces*) *orientalis*. **Teicoplanin** is similar. They are closely related to avoparcin which was used as a production enhancer and has now being withdrawn because of fears about cross resistance with vancomycin.

Acting outside the bacterial cell membrane, vancomycin blocks the transfer of the glycopeptide units from the carrier molecule to the growing polymer peptidoglycan (see penicillin diagram). It is therefore rapidly active.

Almost all Gram positive bacteria are sensitive to vancomycin. It is one of the few drugs effective against methicillin resistant *Staph. aureus* which is why there have been concerns about the possibility of resistance developing. There is complete cross resistance with avoparcin. Almost all Gram negative bacteria are resistant.

High level resistance (*vanA* gene) transmitted on a transposon has been shown to pass between enterococci *in vitro*. There is a danger that these transposons could be passed to other pathogens such as *Staph. aureus*, although this has only been know to occur once in real life. The *vanC* gene, which confers low level resistance, is common in enterococcal chromosomes. A variety of soil bacteria, including some used as insecticides overseas, contain a very similar gene to *vanA*. Vancomycin intermediate *Staph. aureus* use a different mechanism - they have extra thick cell walls so that the drug does not get in easily.

Vancomycin is reserved in people as the last remaining effective treatment against MRSA (although resistance is starting to develop) and for life-threatening enterococcal infections.

Vancomycin must be given by iv infusion, teicoplanin can also be given im. They are not absorbed orally, and are only used orally in the treatment of antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Avoparcin's main use was the prevention of *Cl perfringens* necrotic enteritis in chickens and pigs - bacitracin or avilamycin are now used instead.

Politics

Vancomycin is the drug of last resort for MRSA in people: it should be reserved for this use and **should not be used in animals**. Avoparcin has been phased out as a growth promoter in NZ.

New derivatives of vancomycin are being developed (eg, oritavancin) which circumvent current resistance problems. Do not expect to use them in animals.

Other drugs affecting cell walls

Bacitracin is a complex, cyclical polypeptide with 11 amino acids, isolated from *Bacillus subtilis*. There are over 15 different bacitracins, but bacitracin A is most potent. Commercial preparations tend to be a mixture of various types. It is used as a production enhancer in the US, and to prevent necrotic enteritis in chickens in NZ but has been banned in Europe.

It binds to isoprenyl phosphate in bacteria and prevents this from synthesising the glycopeptide units (N-acetyl glucuronic acid (NAG) - N-acetyl muraminic acid (NAM) pentapeptide isoprene pyrophosphate) produced for construction of peptidoglycan. Bacitracin thereby inhibits bacterial cell wall synthesis. Divalent cations are required for activity, so bacitracin is often complexed with zinc.

Bacitracin is primarily effective against Gram positive bacteria including some *Staphylococcus* spp, *Streptococcus* spp, *Haemophilus influenzae*, *Corynebacterium* spp, *Neisseria* spp, and *Clostridium* spp. It is not clinically effective against enteric Gram negative bacilli. Its main use is to prevent necrotic enteritis in chickens.

Bacitracin has been around since 1947 and is used by the ton without major resistance developing. Individual farms have problems with resistant *Cl perfringens* (chromosomally transmitted efflux pump?) which seems to disappear when bacitracin is not used for several batches of chickens. There is a suggestion that bacitracin may cause the expression of high level resistance to vancomycin in enterococci: this is probably not relevant clinically. Politics are a different matter!

Bacitracin complexes with lipids, including those of mammalian cell membranes, and when given systemically is severely nephrotoxic. Therefore, its use is limited to oral or topical application.

Bacitracin is very poorly absorbed orally, and has been used for gastrointestinal sterilisation. There is no withholding time.

It is also used in combination with other drugs in topical preparations, especially those intended for use in ears and eyes.

Fosfomycin is an old drug which may be revived as it potentiates many other antibiotics.

Cell membrane disruption

Polymixin B is a clinically useful member of the polymixin family of simple polypeptide antibiotics produced by *Bacillus polymyxa*. **Colistin** is a synonym for Polymixin E, when supplied as a sulphomethyl derivative.

Polymixins act as cationic detergents (ie, antiseptics - see also skin pharmacology notes) which interact with the phospholipid bacterial cell membrane causing disruption. As a result, the cytoplasm leaks out and the cell dies immediately. Part of their beneficial action may be through binding of bacterial endotoxins which are also phospholipids. They are included here rather than under disinfectants only because they are produced by micro-organisms.

Polymixin B and colistin produce a rapid kill in most Gram negative bacteria excluding *Proteus* spp. Active growth of the organism is not required. Polymixins are particularly useful in treatment of otitis externa and superficial ocular infections caused by *Pseudomonas aeruginosa*. Acquired resistance is rare. There is complete cross resistance between polymixin B and colistin.

These drugs do not discriminate well between microbial and mammalian cell membranes (ie, they are typical disinfectants / antiseptics). They are concentrated in the renal tubule after systemic administration causing acute renal tubular injury. They are also neurotoxic and cause a non-competitive neuromuscular blockade. Use should thus be restricted to topical applications, although they have been used systemically in the hope that they will mop up endotoxins in equine colic.

Because the molecules are highly charged, no significant absorption occurs after oral or topical administration, even if administered in high doses to inflamed skin.

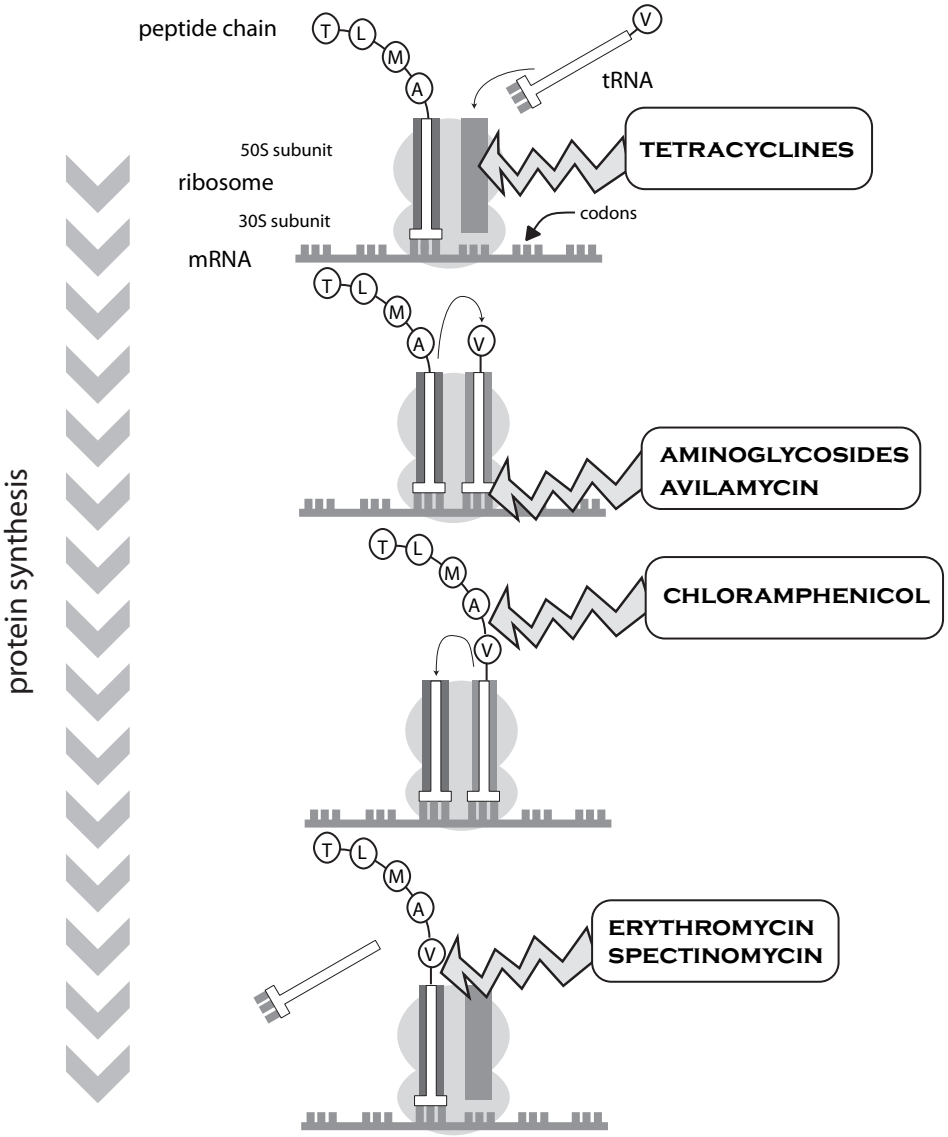
Polymixins are highly bound by other drugs, such as tetracyclines, chloramphenicol, sulphonamides and carbenicillin. **Do not mix them with other drugs** (except if commercially prepared). They are inactivated by divalent cations.

1 mg polymixin B = 8,500 iu, 1 mg colistin = 30,000 iu.

The future?

Neutrophils use a family of polypeptides called protegrins (among other things) to kill bacteria. These are being tried out for topical use in people. A synthetic animal derived protegrin, pexiganin, shows promise. No resistance so far. Iseganin is in phase 3 trials in people with cystic fibrosis. It has a broad spectrum and no resistance has been reported so far.

Protein synthesis



Messenger RNA, transfer RNA and ribosomal RNA are constructed on the DNA template. mRNA codes the ribosome for the amino acid sequence required for construction of a particular protein. Amino acids are then transported to the ribosome by their own particular tRNAs. The amino acid chain is then assembled by transpeptidation. Antibiotics may interfere with several of the steps in this sequence.

Tetracyclines

Oxytetracycline and **chlortetracycline** are used in food animals. **Doxycycline** is sometimes used in small animals: it has better penetration of tissues and binds calcium less tightly than the older drugs. **Minocycline** is similar. Tetracycline itself is not used in animals, although a mixture with lysine, lymecycline is available for use in people.

Mechanism of action

Tetracyclines inhibit aminoacyl-transfer-RNA from binding to the 30S ribosomal subunit-mRNA complex, thereby inhibiting peptide elongation. Tetracyclines enter Gram negative bacteria by passive diffusion through protein pores in the outer bacterial membrane, followed by active transport across the cytoplasmic membrane. This active transport is lacking in mammalian cells, so although tetracyclines inhibit mammalian protein synthesis, therapeutic concentrations are insufficient to affect the mammalian cell. Entry of tetracyclines into Gram positive bacteria is less well understood, but it is known also to involve active transport.

Spectrum of activity

These drugs have a very broad spectrum including Gram negative and Gram positive bacteria, *Mycoplasma*, *Rickettsia*, *Chlamydia* and protozoa. (doxycycline is the drug of choice to treat *Haemobartonella felis*). Tetracyclines are moderately active against anaerobes. They are relatively poor at inhibition of growth of *Proteus* spp. and *Pseudomonas* spp. Overuse has led to resistance, and they are not as clinically useful as previously. Their main use is for *Rickettsia*, *Chlamydia* and some protozoal infections.

Resistance

Resistance to one tetracycline almost always crosses over to all others of this class. Acquired resistance is common. Resistance is conferred by altered permeability / uptake and through production of drug inactivating enzymes.

Doxycycline is used in people for malaria resistant to other drugs; there may well be pressure put on vets not to use it.

Toxicity

Clinically relevant problems

All tetracyclines, but particularly doxycycline, can cause a fatal enterocolitis in horses and are contraindicated, except in cases of rickettsial disease. (They are still widely used in horses in practice though).

Tetracyclines are deposited into the calcifying areas of growing teeth, and growing bone, causing a yellow staining. They also cause temporary cessation of bone growth. Tetracyclines cross the placenta, and can have these effects in the foetus. Therefore, tetracyclines are contraindicated in young or pregnant animals.

Depression and vomiting can occur in most species as direct gastrointestinal effects. Gut disturbances associated with imbalances of the normal flora are also common, especially in ruminants. Supra infections can occur and pseudomembranous colitis has been described.

Tetracyclines are very bitter tasting, and therefore can cause profuse salivation in cats simply due to the taste (as with other bitter drugs). Warn clients that this may occur. Coated tablets are preferred and tablets should not be broken before administration to cats.

Rare problems

Photosensitisation and rashes can occur, especially with doxycycline, although it has also been recorded after oxytetracycline in sheep in NZ.

Cardiovascular collapse can occur after intravenous administration, particularly in cows, probably due to sudden chelation of the plasma ionised calcium.

Tetracyclines can induce fever: drug related fevers can cause confusion when treating infections.

Old tetracyclines beyond their use by date can cause serious renal proximal tubule mal/reabsorption disorders Fanconi-like syndromes. This is caused by a breakdown product.

Tetracyclines can inhibit hepatic drug metabolising enzymes.

Long courses of tetracyclines can lead to vitamin B deficiencies through inhibition of gut flora. For this reason some tablet formulations are combined with supplementary vitamin B.

Tetracyclines can interfere with matrix metalloproteinases and interfere with collagen formation and contraction. Care required in foals.

Pharmacokinetics

Tetracyclines are amphoteric, ie they have both negative and positive charges, although they usually behave as weak acids. They distribute rapidly to all tissues, with good penetration of difficult tissues such as prostate and bone. This is especially true for minocycline and doxycycline, which are highly lipid soluble and distribute to the cerebrospinal fluid quite well. Tetracyclines cross the placenta and distribute to all tissues within the foetus.

Tetracyclines are absorbed quickly but incompletely after oral dosing: most absorption is from the stomach and duodenum. Bioavailability by the oral route is approximately 0.5. They are unstable in acid (except minocycline). Intramuscular injection usually causes irritation (and pain), although this can depend on the vehicle, and absorption can be variable (but see below).

Tetracyclines are easily chelated by divalent cations, particularly calcium, making them insoluble and unavailable for absorption. They should be administered at least an hour before food or antacids. Doxycycline's absorption is much

less effected by foods and divalent cations.

Tetracyclines are protein bound in plasma from 60% (tetracycline) to 95% (doxycycline). They are eliminated by glomerular filtration resulting in 20 - 60% being found unchanged in the urine. They are also eliminated in the bile, and undergo enterohepatic circulation. Small intestinal secretion is the main route by which doxycycline is excreted.

Pharmaceutical considerations

The combination of tetracyclines and penicillins *in vivo* produces true antagonism. Despite this, parenteral procaine penicillin and intrauterine oxytetracycline pessaries are a traditional combination for treatment of post-dystocia uterine infections in cattle. There is clinical evidence that this combination is effective.

Tetracyclines are available in almost any formulation needed for almost all routes of administration. Because of their tendency to chelate cations, care should be exercised when choosing an intravenous fluid for administration by infusion. There are major differences in the non-active formulation ingredients from manufacturer to manufacturer. Products which use propylene glycol or ethanolamine as a vehicle tend to be irritant and cause severe muscle damage. Polyvinyl pyrrolidine (PVP) is better - much less irritant, more reliable bioavailability, less carcass damage but more expensive.

Tetracyclines gradually break down while stored, particularly in sunlight, and out of date preparations should not be used (see toxicity).

Use

Oxytetracycline is used as a cheap, broad spectrum antibiotic, particularly in food animals. It is useful for mycoplasmal diseases such as enzootic pneumonia in pigs.

Doxyclycline is occasionally used for chlamydial or protozoal infections in dogs and cats.

Human use

Doxycycline is the only tetracycline used to any great extent, mainly for mixed infections where *Mycoplasma*, *Chlamydia* or certain protozoa are likely.

Demeclocycline is sometimes used to suppress antidiuretic hormone secretion, as well as for its antibacterial effects.

The future?

Glycylcyclines - tetracycline analogues - are under investigation. They have better activity, particularly against a wide range of resistant organisms. However, some *Salmonella* isolates from animals are already showing resistance.

commonly used drugs

oxytetracycline

Chloramphenicols

Chloramphenicol has been around since 1948, and is still used despite various concerns. Thiamphenicol is very similar (including all the nasty side effects); it is still used in some European countries. **Florfenicol** is a fluorinated analogue of thiamphenicol with major advantages. It has more or less replaced chloramphenicol in most circumstances in veterinary medicine since it lacks most of the side effects. Other derivatives are under development.

Mechanism of action

Chloramphenicols bind to the 50S bacterial ribosomal subunit and inhibits peptide chain elongation by inhibition of peptidyl transferase, the enzyme responsible for peptide bond formation.

Spectrum of activity

Chloramphenicol is bacteriostatic against most Gram negative bacteria except *Pseudomonas* spp. It is also active against many Gram positives, anaerobes, the important *Rickettsia*, *Chlamydia* and some mycoplasmas.

Resistance

Resistance in Gram negative bacteria is plasmid transmitted and is caused by a specific chloramphenicol acetyltransferase which rapidly breaks the drug down. Florfenicol is reasonably resistant to this enzyme. Resistance in Gram positives is caused by a variety of plasmid transmitted acetytransferases. Decreased permeability and decreased sensitivity of ribosomes may also occur. Resistance in *E. coli* and *Salmonella* used to be widespread, but has reduced with decreased use of the drug (1999 - 4.8% of *E. coli* isolates from man resistant). Some bacteria, such as *Salmonella* Typhimurium DT104, show multiple resistance to a variety of antibiotics, including chloramphenicol. These resistance genes are usually passed on as a bunch.

Toxicity

In animals, chloramphenicol can occasionally cause aplastic anaemias, leukaemias and thrombocytopaenias, which are reversible after withdrawal of the drug. It can also cause gastrointestinal upset, both directly and through interference with the normal flora. In cats, vomiting, diarrhoea and anorexia are not uncommon. It has caused superinfections.

The veterinary use of chloramphenicol has been severely restricted as a result of a scare caused by anecdotal reports of a non-dose dependent, irreversible aplastic anaemia in man. This is a fatal condition which is idiosyncratic. On examining the evidence, the WHO found that the overall incidence of chloramphenicol associated aplastic anaemia was less than 1 in 10,000,000 (WHO Technical Report 851, 1995. Evaluation of certain veterinary drug residues in food.) However, because of the scare, chloramphenicol was banned in food producing animals for any reason (although it is still used in people). It remains banned in spite of a lack of scientific evidence that it is harmful. Its use should thus probably be limited to life- or sight-saving applications in companion animals. Owners should be adequately warned to avoid exposure.

Pharmacokinetics

Chloramphenicol's outstanding lipid solubility ensures its distribution to all body compartments including cerebrospinal fluid and the eye. Brain tissue concentrations exceed plasma concentrations.

Chloramphenicol is glucuronated in the liver to an inactive conjugate, but there is no obvious first pass effect, with equivalent oral and intravenous doses achieving approximately the same maximum plasma concentrations. Maximum plasma concentration after oral dosing occurs at about 2 hours.

Approximately 90 - 95% of chloramphenicol is excreted in the urine as the water soluble glucuronic acid conjugate and the remainder as the parent drug. A small amount of the inactive conjugate may be found in the bile. Alterations to hepatic microsomal enzymes may alter the elimination rate of chloramphenicol, and result in accumulation to toxic levels. Chloramphenicol also inhibits hepatic mixed function oxidase enzymes (cytochrome P450s) and may therefore cause accumulation of other drugs being co-administered, eg, phenobarbitone, phenytoin. Elimination is very rapid in horses, slow in cats. Accumulation can occur in cats.

Use

Dogs and cats - ointment for eye infections.

Florfenicol has the potency and spectrum of chloramphenicol, but without the toxicity (the main side effect is anorexia). It is unaffected by chloramphenicol acetyltransferase, so is active against some chloramphenicol resistant bacteria. It is sold as an injectable solution for respiratory infections in cattle, but should not be used in bulls as it causes testicular atrophy in most species (at high doses).

It was developed in the USA for *Pasteurella* pneumonia which had become resistant to penicillin from overuse. Its role in NZ, where this sort of pneumonia is rare, is not yet clear. It can also be used as eyedrops in horses and companion animals.

Human use

Chloramphenicol is used as an ointment for eye infections and as an antibiotic of last resort.

Macrolides and similar drugs

These drugs have different chemical structures but are clinically very similar in their pharmacokinetics and spectrum of action. They are all bacteriostatic.

Macrolides include **erythromycin**, **tylosin**, **tilmicosin** and **spiramycin** (less active) which are commonly used in animals; **oleandomycin** is sometimes used in people. **Roxithromycin**, **clarithromycin** and **azithromycin** are new human drugs which look promising (better pharmacokinetics). Kitsamycin is used in animals in Australia.

Lincosamides are chemically different but clinically identical to macrolides. **Lincomycin** and **pirlimycin** are used in animals, **clindamycin** in people.

Pleuromutilins are also very similar. **Tiamulin** is the only drug used in NZ, but valnemulin is used in Europe. **Retapamulin** has recently been approved in the USA and EU for Staph skin infections in people and there may be pressure in the future to reduce pleuromutilin use in pigs.

Mechanism of action

Bind to the 50S bacterial ribosomal subunit and inhibit peptide chain elongation by inhibition of translocation and movement along the mRNA.

The macrolides have recently been shown to have some anti-inflammatory effect - preventing superoxide and cytokine production and stabilising macrophages and T cells. This may be a useful side effect in respiratory and skin infections.

Erythromycin acts as a prokinetic in the bowel by several mechanisms (see gut pharmacology notes).

Spectrum of activity

These drugs have a narrow spectrum mainly confined to Gram positive bacteria, including penicillinase producing staphs, but not enterococci. They are also active against *Pasteurella* and *Bacteroides* spp, *Mycoplasma* spp and *Rickettsia* spp. Tylosin and roxithromycin are used clinically against *Mycoplasma*, *Chlamydia* and some spirochaetes (*Treponema* and *Moraxella*). Tiamulin is effective in swine dysentery (*Brachyspira hyodysenteriae*). Most strains are now resistant to tylosin. Erythromycin is effective against *Rhodococcus equi* in foals. Macrolides (especially erythromycin) are used in people for severe *Campylobacter* infections, but resistance is high and increasing (particularly around Auckland). Roxithromycin and azithromycin have some activity against protozoa such as *Toxoplasma gondii*. Lincosamides, particularly clindamycin, have useful activity against anaerobes.

Resistance

Chromosomal resistance occurs readily. Plasmid mediated resistance is also common. Resistance usually involves changes to the 50S ribosomal unit which prevents drug binding. This occurs very quickly with lincosamides and slowest with tiamulin.

Cross resistance amongst the macrolides, lincosamides and streptogramin Bs is common but not complete.

Pleuromutilins bind to several different sites so resistance develops more slowly, and there is less cross resistance.

Toxicity

Macrolides are generally safe unless given rapidly iv when they can cause arrythmias. Tilmicosin is is probably worst and should not be given iv. None of the species we deal with are as bad as people, but care is still required. Some local reactions occur at the site of injection, especially thrombophlebitis after intravenous injection. Horses tend to get gastrointestinal disturbances due to enterohepatic circulation and the antibiotic effect on the normal flora. Tylosin is contraindicated in the horse for this reason.

Dogs and cats often get gut upsets and vomiting after erythromycin (it increases gut motility (see gut notes)).

Tilmicosin is cardiotoxic and must not be given iv, although arrhythmias have been reported with most of these drugs in people.

Tiamulin in combination with coccidiostats will cause severe growth depression (mainly important in pigs).

Transient deafness has been reported in people.

Pharmacokinetics

The macrolides are organic bases. Erythromycin's pKa is 8.6 and tylosin's pKa is 7.1 so their action is favoured by higher pH.

Erythromycin is absorbed poorly after oral administration, but distributes well to many tissues, achieving higher tissue concentrations than plasma. This is especially true for bone. Macrolides are also taken up by phagocytes. They do not penetrate the intact blood brain barrier. Ion trapping ensures that macrolides achieve high concentration in normal milk, but the raised pH of mastitic milk reduces the benefit of this effect.

Macrolides are found in saliva at high concentrations. One product (Stomorgyl) is a combination of the macrolide spiramycin with the nitroimidazole metronidazole. This product is marketed strongly on the basis of saliva penetration.

Macrolides undergo extensive enterohepatic circulation. They are largely metabolised and only small amounts can be found in the urine or the faeces.

Lincosamides are rapidly and almost completely absorbed after oral administration with peak plasma levels occurring within 2 hours. Clindamycin is better absorbed than lincomycin.

Clindamycin is 90 -95% plasma protein bound. It is distributed widely, but is not concentrated in any particular tissue. It does cross inflamed meninges and passes into bone, achieving about 40% of plasma concentration in these tissues (humans). Liver metabolism produces active and inactive metabolites. Most drug is eliminated by the liver, with only 8 - 20 % being excreted in the urine.

Azithromycin has a very long half life (35h) in cats so is usually given as a single dose. It is extensively bound in tissues.

Pharmaceutical considerations

Erythromycin is acid labile and must therefore be administered as enteric coated tablets, or parenterally. Estolate and stearate salts are used to enhance absorption. Newer macrolides such as roxithromycin have been designed to overcome this problem.

Tylosin is available as a powder for mixing with drinking water. This is used especially in the poultry industry. Tylosin is also available as parenteral preparations in some countries. It has been banned in Europe as a growth promoter.

Use

cattle - Pasteurella pneumonia (rare in NZ although almost ubiquitous in feedlots in the USA)

pigs - treating and preventing respiratory infections (pleuropneumonia and enzootic pneumonia) and dysentery (especially tiamulin).

chickens - chronic respiratory disease caused by *Mycoplasma*

small animals - skin infections, osteomyelitis, anaerobic infections, (toxoplasmosis)

horses - Rhodococcus pneumonia in foals (azithromycin), otherwise best avoided

Human use

Erythromycin has traditionally been used as a subtitute for penicillin in people who are allergic to penicillin. It was also used to treat *Campylobacter*, but overuse as part of a protocol for *Helicobacter* means that many strains of *Campylobacter* in NZ are now resistant.

Azithromycin is usually reserved for chlamydial infections, but has been used in antimalarial combinations with chloroquine. Clarithromycin has some effect against TB, and is included in some protocols for multiresistant TB.

The future?

The 3-ketolides are a new related group of drugs which look promising. Telithromycin has been licensed for human use overseas and appears effective against erythromycin resistant *Strep pneumoniae*. However, there have been a few cases of liver disease attributed to it, so this may discourage its use.

commonly used drugs

small animals - erythromycin
pigs & chickens - tylosin, tiamulin
cattle - tilmicosin

Streptogramins

Virginiamycin was used as a production enhancer in animals; it is now only licensed for treating necrotic enteritis in chickens where nothing else is likely to work, and for preventing laminitis in horses. (It is supposed to alter gut flora, which results in less of whatever causes laminitis circulating to the feet.) Pristinomycin has been in human use in France for many years. It has to be given orally as it is not water soluble enough for parenteral use. **Quinupristin & dalfopristin** (RP59500, "Synercid") is a new drug used against methicillin resistant *Staph aureus* in people (not in general use in NZ yet).

The nomenclature of this class of drugs is confusing as they are all synergistic mixtures of at least two different compounds. Thus virginiamycin is 75% virginiamycin M1 (a streptogramin A) and 5% virginiamycin S1 (a streptogramin B). The two drugs are structurally unrelated (streptogramin Bs are macrolides), bind to distinct sites of the 50 S ribosomal subunit, but cooperate to inhibit protein synthesis. The mechanism of inhibition is different for each component, however binding of Type A leads to a conformational change in the 50S subunit which potentiates the action of Type B streptogramin. Individually the molecules are only bacteriostatic, but together they act synergistically and are bactericidal.

Spectrum

Bactericidal against Gram positives.

Resistance

A single gene confers cross resistance among the macrolides, lincosamides and streptogramin Bs, but the streptogramins as a combination are not usually affected. There is complete cross resistance between virginiamycin and quinupristin & dalfopristin.

Toxicity

Bacterial overgrowth leading to haemorrhagic diarrhoea has been reported. Rarely, lung oedema has been associated with virginiamycin.

Pharmaceutical considerations

Virginiamycin is practically insoluble and so is only given orally for its effect on gut flora, pristinomycin is available in injectable form. Virginiamycin has recently been banned in Europe.

Indications

Virginiamycin is licensed in NZ for prevention of laminitis in horses and necrotic enteritis in chickens where nothing else is likely to work. In view of the cross resistance with a drug of last resort in people, this is ethically dubious. The other streptogramins **should not be used in animals**, and should be reserved for MRSA in people.

Aminoglycosides

Streptomycin, **dihydrostreptomycin**, **neomycin** (a mixture of neomycin A, B and C), **gentamicin** and **Framycetin** (neomycin B) are used in animals. **Amikacin**, **tobramycin**, and **netilmicin** are used in people. Kanamycin and sisomicin are obsolescent human drugs. **Paromomycin** is occasionaly used to treat *Cryptosporidia*.

nb. Gentamicin and netilmicin are spelt differently from the others because they are derived from different fungi (*Micromonospora* rather than *Streptomyces*).

The related antibiotics, **spectinomycin** and **apramycin** are usually classified as aminocyclitols. They are similar in most respects to aminoglycosides.

Mechanism of action

Aminoglycosides bind tightly to the 30S ribosomal subunit, and block peptide synthesis by preventing tRNA attachment, blocking normal initiation, and distorting the codon arm to cause mismatching of the codon-anticodon couples. This latter action results in the production of so-called "nonsense peptides". Penetration of the cell (and thus activity) is greatly aided by drugs which interfere with cell wall synthesis such as ß-lactams.

Spectrum of activity

Aminoglycosides are rapidly bactericidal against Gram negative aerobic bacteria, and have some useful activity against Gram positive aerobic bacteria such as staphs. Streptomycin is also active against *Mycobacterium bovis* and tuberculosis in people. Gentamycin, tobramycin and the newer aminoglycosides are effective against *Pseudomonas* spp.

Aminoglycosides are ineffective against anaerobic bacteria because uptake requires oxygen dependent transport processes.

Synergism with penicillins and cephalosporins can occur in some circumstances, and is probably due to damage to cell walls allowing penetration of the aminoglycoside. This is especially useful to extend the spectrum of activity of aminoglycosides to include Gram positive bacteria. However,

they are usually chemically incompatible, so do not use home made mixtures.

Resistance

Resistance to aminoglycosides develops relatively quickly, either by chromosomal mutation or by acquisition of plasmids. Resistance is caused by enzymes which degrade the antibiotic, alterations to the ribosomal binding protein, or of bacterial permeability to the antibiotic. Some bacteria have broad spectrum resistance to the aminoglycosides, others are specific for an individual drug. Gentamicin is most likely to develop resistance; amikacin is least likely. Thus cross resistance is likely but difficult to predict. Adaptive resistance has been demonstrated with the aminoglycosides. *Pseudomonas* develops resistance relatively quickly, staphs more slowly and coliforms very slowly.

Toxicity

Two toxic syndromes are clinically important:

renal proximal tubule epithelial cell injury resulting in acute renal failure (This is the major limiting factor on their use in veterinary practice.)

vestibular and / or cochlear injury resulting in cranial nerve VIII signs.

All aminoglycosides can cause renal damage, especially if pre-existing renal disease exists, or if the animal is dehydrated, or if aminoglycosides are given with frusemide. Serial monitoring of serum creatinine is recommended. Therapeutic drug monitoring is valuable. Care should be taken to allow plasma drug levels to fall to troughs less than 2 mg/ml for several hours each day. Toxicity is associated with high trough drug levels more than with high peak drug levels. In practice, once a day dosing with its peaks and troughs is safer and just as effective as maintaining steady plasma levels by more frequent dosing - peak concentration is what counts for killing bacteria rather than time above MIC.

Deafness may be irreversible. Dihydrostreptomycin and amikacin are most likely to cause ototoxicity.

Aminoglycosides can also cause competitive neuromuscular blockade, especially when given with anaesthetics or other NMJ blockers.

Pharmacokinetics

Aminoglycosides are organic bases and are more active at higher pH. They are very polar at plasma pH and are therefore distributed only to body water. They do not penetrate cell membranes and are not absorbed to any great extent after oral administration.

Parenteral administration results in rapid absorption and distribution. Aminoglycosides are cleared from the plasma rapidly by glomerular filtration, but are accumulated by the renal proximal convoluted tubule cells, and may persist in the kidneys for months after a single injection - **residues**!

Since antibacterial efficacy depends on peak concentration reached and kidney damage depends on the time allowed for elimination between doses, it is now usual to give gentamicin in a high dose once daily rather than a small dose three times daily as used to be recommended.

Pharmaceutical considerations

Neomycin is too toxic for parenteral use (although available in NZ!), and is only used in topical preparations or orally for gastrointestinal "sterilisation".

Sulphate salts improve solubility, but solutions tend to be quite acidic, so may sting when administered im or sc and when given iv must be diluted and given slowly.

Use

Aminoglycosides are falling out of favour because of residues (food animals) or toxicity (companion animals). Gentamicin is still widely used in horses. Although its spectrum of activity is mainly Gram negative, gentamicin is sometimes useful for ß-lactamse producing staph infections. It is also the drug of choice to treat *Pseudomonas* infections.

Aminoglycosides are widely abused in young food animals to treat diarrhoea. Calves and piglets with diarrhoea need fluids, not antibiotics.

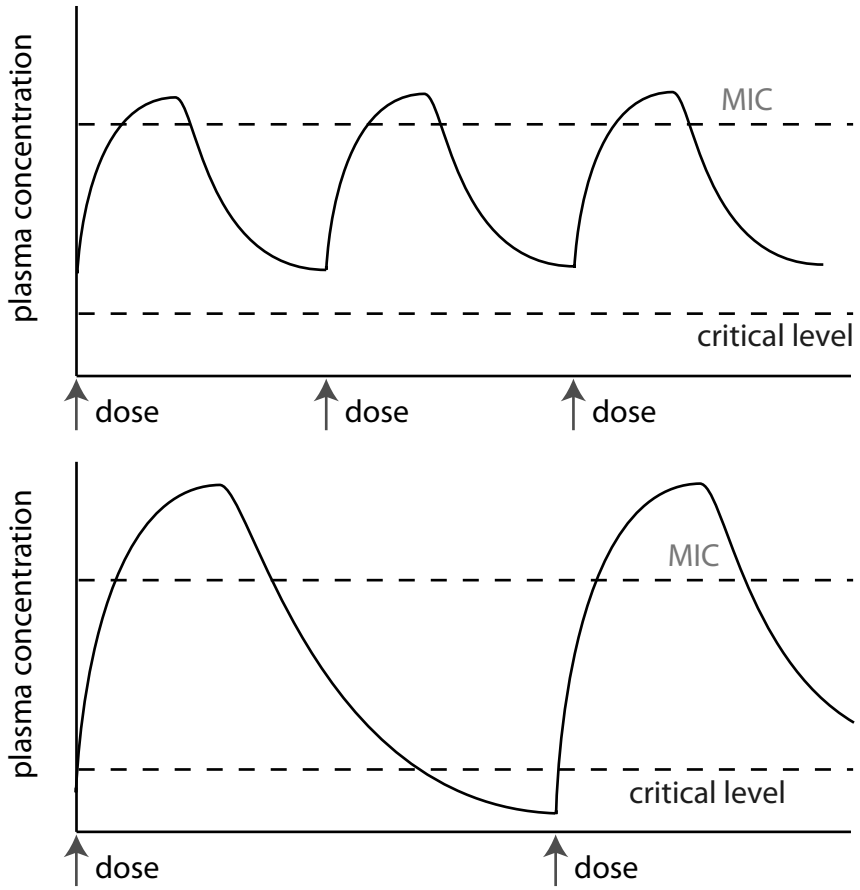
Lots of streptomycin is sprayed on apple trees and tomatoes in NZ to treat fireblight and bacterial wilt, although this practice is on the decline since it was banned in Europe.

Human use

A variety of the newer aminoglycosides are important in treating serious Gram negative infections. Streptomycin went out of fashion because it made people deaf, but is becoming important again as part of a multiresistant TB combination.

commonly used drugs

streptomycin
neomycin
gentamicin



Less frequent dosing with a bigger dose allows a higher peak concentration and also allows the plasma concentration to fall below the critical level for accumulation in the kidney and ears.

Avilamycin

Avilamycin is only used to prevent necrotic enteritis in chickens. Avilamycins are oligosaccharides and are usually classified as orthosomycins. There are many closely related orthosomycins, such as the everninimicins, flambamycin, curamycin and sporosuracins, none of which are used clinically in humans or animals in NZ at the moment.

Avilamycin binds to the bacterial 30S ribosomal subunit and inhibits the attachment of tRNA, in a similar manner to aminoglycosides. The avilamycins are only active against Gram positive bacteria.

SCH27988 (Ziracin), an everninomicin which is very similar to avilamycin, looked promising at one time for Gram positive nosocomial infections in people. It was active against a wide range of multi resistant staphylococci, enterococci and streptococci, but has now been dropped for safety reasons.

Avilamycin is used as a growth promoter in pigs and chickens overseas. Avilamycin is useful against *Cl. perfringens* (necrotic enteritis) which is resistant to bacitracin.

There appears to be complete cross resistance between avilamycin and everninomycins in enterococci isolated from broiler chickens and pigs. Resistance appears to develop slowly, both *in vitro* and in the field.

Avilamycin is the only growth promoter left for chickens in Europe, where it is now used by the thousands of tons. Any problems should show up quickly there (none so far). It is not used much in NZ - at the moment.

Fusidic acid

Fusidic acid is a lipophilic steroid antibiotic derived from the fungus *Fusidum coccineum*. It inhibits binding of aminoacyl tRNA to the ribosome so inhibiting protein synthesis. It may be bacteriostatic or bacteriocidal. It is usually used as the sodium salt (sodium fusidate).

It causes liver toxicity when given parenterally, so is usually given orally or topically. Oral fusidate is well absorbed and tends to be concentrated in bone. Effective against Gram positives, mainly staphs (including MRSA). Streps and enterococci are not susceptible. Also has some antiprotozoal and antiviral properties and immunosuppressant actions. It is often impregnated into wound dressings.

Resistance develops rapidly *in vitro*, but has not been a problem in real life so far.

Although it has been used for trivial infections in the past, it is starting to be reserved for MRSA in human medicine - vets beware.

Oxazolidines

The oxazolidines are a completely new class of antibiotic - the first for many years. **Linezolid** has just been approved in NZ for people. It is effective against all Gram positive organisms with no resistance reported so far. It is likely to be reserved in people for MRSA and VRE infections (its current use in NZ) and possibly multirresistant TB. **Do not use in animals**.

Mupirocin

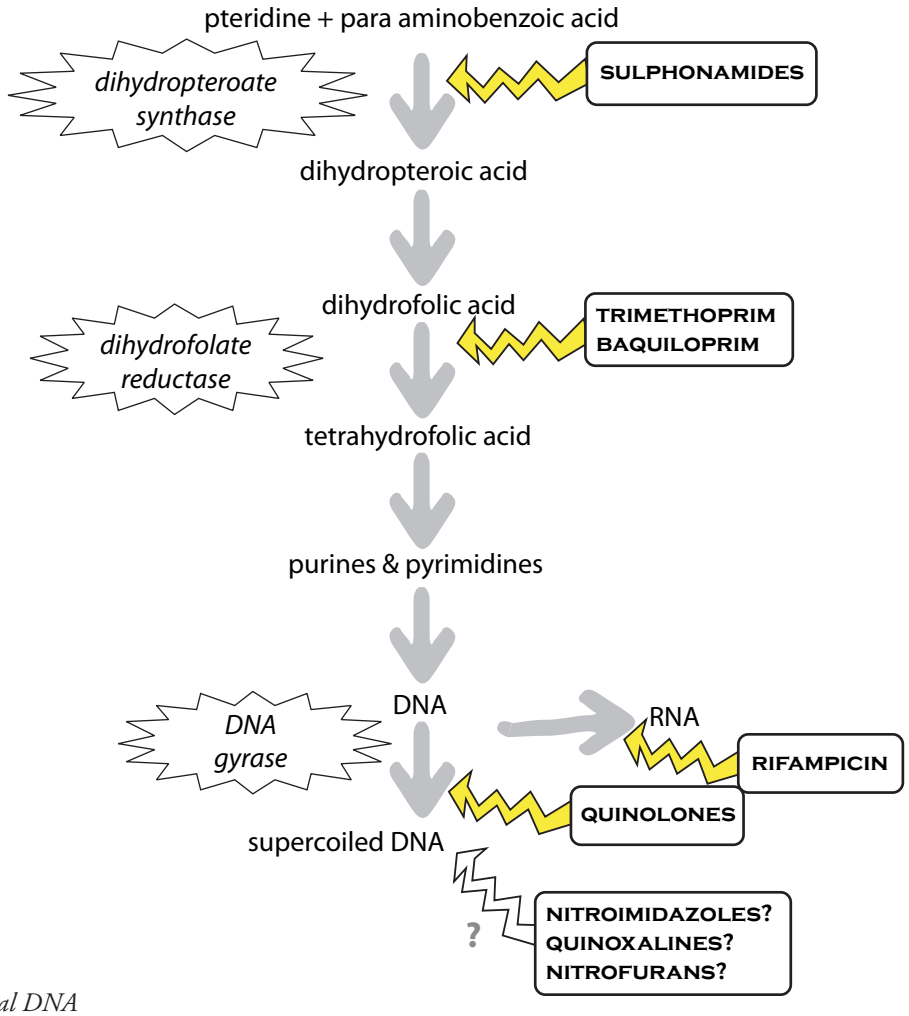
Mupirocin inhibits bacterial protein synthesis by binding to isoleucyl tRNA synthetase. It is bacteriostatic at low concentrations and bacteriocidal at high concentrations.

It is only used topically as it is rapidly metabolised if absorbed.

It is mainly used against staphs (particularly MRSA) and streps, but also has activity against *Candida*.

In NZ, it was reserved for treating MRSA until recently, when widespread resistance has made it almost useless.

Nucleic acid synthesis



Synthesis of bacterial DNA

Sulphonamides

The sulphonamides were the first group of completely synthetic antimicrobial drugs (ie, strictly speaking they are antibacterials rather than antibiotics). They are rarely used alone these days because of resistance. **Sulphadiazine** and **sulphamethoxole** are often mixed with trimethoprim (dihydrofolate reductase inhibitor, see next section) to form **co-trimazine** and **co-trimoxazole**. Mixtures with baquiloprim are sometimes also used. There is not much difference between sulphonamides except in solubility and pharmacokinetics.

Mechanism of action

The pyrimidine thymine is a necessary precursor for DNA synthesis. In the absence of thymine or thymidine in the media, bacteria are able to synthesise pyrimidines from the precursor para-aminobenzoic acid (PABA), through the folic acid cycle. In the absence of thymidine, inhibition of its synthesis results in inhibition of cell replication, growth, and DNA repair. (Mammalian cells get their folate as a vitamin from food.)

Sulphonamides act by competitively inhibiting the incorporation of PABA into folate. Since it is a competitive inhibition, the presence of large amounts of the substrate PABA reduces the efficacy of these antimicrobial drugs. Also, if the bacterial media contains thymine, or thymidine, these can be used for DNA synthesis directly and sulphonamides will have little effect.

Spectrum of activity

These are broad spectrum antimicrobial drugs, but the spectrum has been compromised by widespread resistance. They are primarily bacteriostatic against Gram positive bacteria, excluding *Staphs.* Sulphonamides are also effective against many types of protozoa such as coccidia. The combination with trimethoprim or baquiloprim is bactericidal.

Sulphonamides may be effective in treatment of infections by *Streptococcus* spp., *Salmonella* spp., *E. coli*, *Pasteurella* spp., *Shigella* spp., *Actinomyces*, *Nocardia*, *Chlamydia*, *Toxoplasma*, and *Plasmodium* but the effect is not reliable because of resistance (see below).

Resistance

Chromosomal resistance develops slowly, but rapidly induced plasmid mediated resistance is commoner. Possible mechanisms: reduced drug penetration, increased production of PABA or reduced sensitivity of dihydropteroate reductase.

Resistance is widespread and severely limits the use of sulphonamides - they must be potentiated with dihydrofolate reductase inhibitors in most cases to be effective. There is complete cross resistance among sulphonamides.

Sulphonamides are inactivated in pus, which can lead to a lack of clinical efficacy.

Toxicity

Older forms of sulphonamide were less soluble and often crystallised out in the urine. With newer drugs this is less of a problem. Nevertheless, patients must be adequately hydrated to ensure dilute urine.

Sulphonamides often cause hypersensitivity reactions. Sulphonamides or potentiated sulphonamides are the main cause of adverse drug reaction in people in NZ. Their use in people is rare now for this reason. Photosensitisation or rashes, blood dyscrasias and hepatopathies occur, but are usually reversible by stopping the drug. These probably occur in animals too but are not noticed.

Sulphonamides can cause keratoconjunctivitis sicca in dogs after prolonged administration (mechanism unknown but probably immune mediated). Immune mediated polyarthritis has been reported in Dobermanns.

Sulphonamides in ruminants can cause suppression of ruminal flora. Prolonged treatment can reduce vitamin K production leading to haemorrhage (especially in poultry).

Sulphonamides can also cause thyroid supression (cf propylthiouracil - a sulphonamide). Reduced thyroid hormone production causes increased TSH secretion which can cause thyroid tumours.

Combination with dihydrofolate reductase inhibitors mean that much smaller doses need to be given, which reduces the incidence of all but hypersensitivity side effects.

Pharmacokinetics

With the exception of some drugs which were synthesised particularly for use in the lumen of the gastrointestinal tract (and are thus not absorbed, e.g. sulphasalazine, sulphaguanidine, phthalysulphathiazole) sulphonamides are absorbed well and rapidly after oral administration.

Sulphonamides are distributed rapidly to all tissues, including the eye and the cerebrospinal fluid. There are differences in distribution between drugs, and sulphadiazine is best distributed to the CNS.

Sulphonamides are weak acids, and are therefore more active in acidic environments.

Free sulphonamides and hepatic metabolites (acetylated derivatives) are eliminated by both glomerular filtration and tubular secretion. Longer acting forms achieve their lower clearance by being more highly protein bound and by being reabsorbed by the renal tubule.

Acetylation of sulphonamides increases the chances of crystalluria. The extent of acetylation is greatest in man > ruminants > horse > cat. The dog does not acetylate sulphonamides. Of the two most commonly used sulphonamides (in preparations with diaminopyrimidines; see below) in those species which acetylate sulphonamides, sulphamethoxazole is more likely to cause crystalluria than sulphadiazine.

Sulphonamides are often classified on the basis of the pharmacokinetics, specifically half life:

Short acting
- sulphanilamide
- sulphacetanide
- **sulphadiazine**
- sulphadimidine (=sulphamethazine)
- sulphafurazole (=sulfisoxazole)
- sulphachlorpyridazine

Medium acting
- **sulphamethoxazole**

Long acting
- sulphamethoxypyridazine
- sulphadimethoxine

Ultra long acting
- sulphadoxine

This classification must be kept flexible because of species differences.

Sulphasalazine is sulphapyridine complexed with salicylic acid. It is sometimes used in chronic large bowel disease where bacteria break down the complex. It is thought that the salicylic acid probably produces all the useful effects.

Pharmaceutical considerations

Sulphonamides are often formulated as sodium salts to increase their solubility. Monosodium salts are very irritant to tissues, and must be given iv only. Disodium salts can be given im, ip etc.

The "law of independent solubility" means that the presence of one drug in solution does not affect the solubility of another drug. However, the antimicrobial action of the different sulphonamides is additive. Therefore, combination of several sulphonamides together can reduce the dose of each, thereby reducing the potential for toxicity, without compromising the antibacterial efficacy.

Drug interactions

B vitamins and their precursors (and related amino acids such as methionine) antagonise sulphonamides. Some drugs such as procaine have PABA as a major metabolite and will do the same.

Use

Sulphonamides on their own are really only (ab)used to treat scours in calves and piglets. Potentiated sulphonamides are still amongst the most commonly used broad spectrum antibiotics in veterinary medicine - they are cheap!

Human use

Not used much any more because of side effects. Even so, sulphonamides and trimethoprim account for over half of all drug adverse reactions in NZ.

Similar drugs

Other sulpha-like drugs include sulphones, e.g. **dapsone, sulphoxone**. These are bacteriostatic or bactericidal to *Mycobacteria* spp. They are used in people for leprosy, but have been used in cows for mastitis and have the same spectrum of activity as sulphonamides. Concerns about residues mean that they should not be used in food animals (dapsone is potentially carcinogenic).

Sulphamylon has been used topically to prevent infections of burns.

Dihydrofolate reductase inhibitors

Trimethoprim is a diaminopyrimidine analogue of para aminobenzoic acid. A very similar drug, **baquiloprim**, is also used in cattle and pigs because trimethoprim has a short half life in these species. They are nearly always used in combination with sulphonamides (potentiated sulphonamides).

Mechanism of action

Trimethoprim acts by inhibiting the enzyme dihydrofolate reductase. This results in failure to reduce dihydrofolate to tetrahydrofolate, thereby blocking pyrimidine synthesis and potentiating the effects of sulphonamides.

Spectrum of activity

Trimethoprim has a similar spectrum of activity as sulphonamides. The two agents are probably synergistic in most circumstances. Trimethoprim is used alone in urinary infections in people, where it appears that sulphonamides do not contribute to its effect.

Resistance

Plasmids encoding trimethoprim resistant dihydrofolate reductases can be passed on and become incorporated in the chromosomal DNA. Some bacteria just overproduce dihydrofolate reductase. Cell wall permeability to trimethoprim may also reduce and some bacteria have learned to rely on exogenous thymine and thymidine as mammals do.

Clinically, resistance exists but is not a huge problem.

Toxicity

Blood dyscrasias (anaemia) occur rarely and are usually reversible by stopping trimethoprim or giving folate. Trimethoprim may cause an increase in serum creatinine through inhibition of renal secretion. Several cases of hypersensitivity in Dobermanns and Great Danes have occurred with polyarthritis, pyrexia, anorexia and depression. This was probably caused by the sulphonamide component of the mixture.

All the side effects of sulphonamides can occur with potentiated sulphonamides as well.

Pharmacokinetics

Trimethoprim is usually administered with sulphamethoxazole (co-trimoxazole) or sulphadiazine (co-trimazine) at a fixed dose ratio of 1:5. The pharmacokinetics of trimethoprim and sulphamethoxazole are closely matched when given independently in most species. However, trimethoprim tends to slow the absorption of sulphamethoxazole. These kinetic interactions vary between species. High levels are areached in the urine and CNS.

Trimethoprim is more slowly eliminated than short acting sulphonamides in most species. Therefore the combination with sulphamethoxazole seems more rational, especially in the dog where acetylation of sulphamethoxazole is not a problem. The half life of trimethoprim in cattle is about 30 min, so baquiloprim, with a half life of 10 hours, seems a more rational choice.

Similar drugs

A variety of dihydrofolate reductase inhibitors are used against protozoa. **Pyrimethamine** is more specific for protozoal dihydrofolate reductase and was commonly used for malaria in man, and occasionally for *Toxoplasma* or similar organisms in animals. **Methotrexate** is more specific for mammalian dihydrofolate reductase and is used as an anticancer drug (qv).

Current research is concentrating on dihydrofolate reductase inhibitors which are more specific for Gram positives, specifically MRSA. There are a number of promising drugs coming along.

commonly used drugs

co-trimoxazole
co-trimazine

Fluoroquinolones

Fluoroquinolones are derived from nalidixic acid, which itself has fallen from use because of neurotoxicity problems. The fluoroquinolones are one of the newest groups of antibiotics (at least in veterinary medicine) and therefore subject to most market hype. **Enrofloxacin**, **marbofloxacin**, **orbifloxacin**, sarafloxacin and danofloxacin are registered for veterinary use in NZ. **Norfloxacin** and enrofloxacin's main metabolite **ciprofloxacin** are in human use in NZ. The newer generation fluoroquinolones (8-methoxyfluoroquinolones), such as **levofloxacin**, **moxifloxacin** and **gatifloxacin**, have recently reached NZ for human use They have greater Gram positive activity (particularly for *Streps*) and kill many resistant bacteria. However, fluoroquinolones are the main drugs for Gram negative infections in people and there will be pressure from the medical profession to reduce their use in animals to slow the development of resistance.

Mechanism of action

Bacterial DNA normally forms superhelical twists under the influence of the enzyme DNA-gyrase (topoisomerase II) (most important in Gram negatives) and topoisomerase IV (most important in Gram positives). DNA gyrase and topoisomerase IV are composed of four subunits; two each of GyrA and GyrB, and ParC and ParE respectively. The enzymes bind to the DNA, cut it, then allow a stand to pass through and join the DNA again (see diagram). This process of winding and unwinding is necessary for protein binding to DNA such as occurs in DNA transcription and DNA repair. Fluoroquinolones inhibit DNA-gyrase and topoisomerase IV (the balance of effects being different with individual drugs), resulting in failure of DNA super helix formation and management. This happens in two stages - the fluoroquinolone binds to the enzyme - DNA complex (bacteriostatic) then causes the release of unjoined DNA (bacteriocidal). Other mechanisms may also be involved in the bactericidal action. This may partly account for high concentrations of quinolones having less bactericidal activity (*in vitro*).

Fluoroquinolones have been shown to cause a marked post-antibiotic effect, ie, a continued bacterial growth inhibition in those bacteria surviving after the removal of the drug from the bacterial media. Nevertheless, the rate of bactericidal action is proportional to the length of time above MIC, so efficacy might be improved by increasing dose frequency above that recommended.

Spectrum of activity

Ciprofloxacin and enrofloxacin are mainly active against aerobic Gram negative organisms, but are not very active against Gram positive aerobes (except for reasonable activity against *Staphs*) or anaerobic organisms. They are reasonably active against *Mycoplasma*. Some activity is reported against *Pseudomonas*, *Rickettsia*, *Chlamydia*, and *Mycobacteria*. Newer drugs (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin, and trovafloxacin) have more activity against Gram positives, especially *Streps*.

Resistance

Fluoroquinolone resistant isolates usually contain one or more mutations in a small section of GyrA or ParC; mutation in GyrB and ParE is rare, but getting commoner. In Gram negative bacteria, where mutations have given rise to a resistant DNA gyrase (low level resistant), mutations then occur in the topoisomerase IV genes (and vice versa for Gram positive bacteria) to give a highly resistant bacterium. Newer drugs which inhibit both enzymes give rise to less resistance.

In addition, there are genes that influence the uptake of the drug into the bacterial cell and efflux pumps that can be over expressed to enhance excretion of quinolones from the cell. This enhanced efflux in turn causes increased MICs of several drugs, including fluoroquinolones, tetracycline, chloramphenicol, and ampicillin. It has been suggested that mutations enhancing efflux occur as a first step, allowing the bacteria to survive so that mutations can accumulate in genes encoding the target proteins. Plasmid mediated, transferable fluoroquinolone resistance has recently been described; its mechanism of resistance is by coding for a protein that binds the drug and inactivates it.

Clinically significant resistance occurs in *Pseudomonas*, *Staph aureus* and *Campylobacter*. The resistance in *E. coli* isolated from dogs in NZ is rising at a much faster rate than that in *E. coli* isolated from people here.

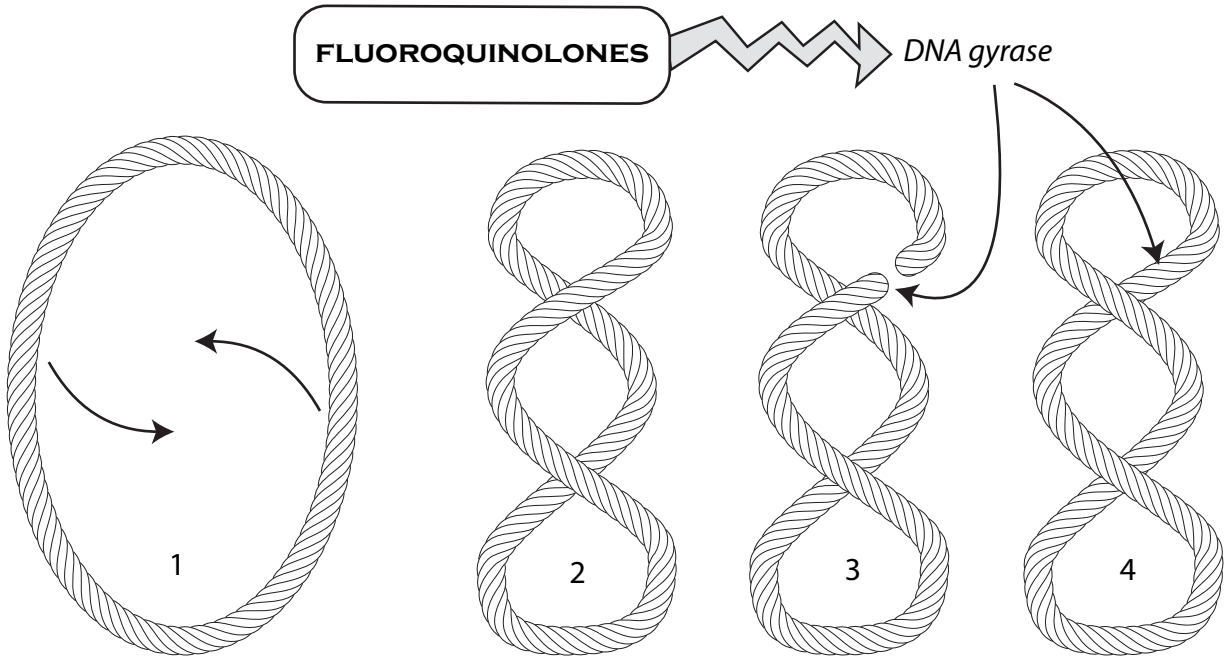
Toxicity

Mammals do not super coil their DNA so these drugs are relatively safe. Injury to growing articular cartilage in young animals (dogs are most sensitive) occurs - usually at high doses. Use in children has shown reversible joint pain in 1.5% of cases, but there is *in vitro* evidence of chondrocyte damage in adults. There is a small risk of tendonitis in old people, especially when combined with steroids. Avoid use in young animals if possible. Nausea, vomiting and diarrhoea are the commonest side effects in people.

Very high doses may cause embryonic losses in some species and ocular damage in dogs, although intravitreous injections have been used in people. Retinal damage has been reported in cats at clinical doses of enrofloxacin and it is now recommended to avoid enrofloxacin in cats and certainly do not give more than 5mg/kg. Orbifloxacin does not appear to cause this problem, but experience is limited.

Fluoroquinolones can block $GABA_A$ receptors (although some drugs are worse than others - norfloxacin worst, ofloxacin best), and this effect is potentiated by NSAIDs. Enrofloxacin can induce hallucinations and rarely convulsions in humans (ofloxacin is used instead). Fluoroquinolones should probably not be given to animals with a history of seizures.

Photosensitivity (potentiation of the effects of UVA) and tachyarrhythmias have been recorded in people.



The folding of bacterial DNA and the action of DNA gyrase and the fluoroquinolones.

Pharmacokinetics

Fluoroquinolones exhibit variable gastrointestinal absorption in most species, with food inhibiting absorption. Concomitant administration of antacids containing magnesium or aluminium, or of sucralfate almost completely prevents oral absorption.

Oral bioavailability of enrofloxacin in foals appears to be good, but chondrotoxicity prevents its use.

Norfloxacin is inactivated at pH < 6.8 and may cause crystalluria in alkaline urine.

Fluoroquinolones are partially metabolised in the liver and are excreted as both active and inactive metabolites (ciprofloxacin is the major active metabolite of enrofloxacin), and as parent drug. They may be found in both the bile and urine at 20 times the plasma concentration.

Fluoroquinolones are rapidly and widely distributed to many tissues including prostate, testes, urinary bladder wall, renal parenchyma, uterus, gall bladder, and to the CSF across healthy or inflamed meninges. They are actively concentrated in neutrophils, which may carry the drugs to the site of infection. Topical norfloxacin can penetrate all chambers of the eye to concentrations above MIC for most pathogens.

Doses of fluoroquinolones should be reduced in renal failure.

Pharmaceutical considerations

Drugs which inhibit protein synthesis, eg rifampicin and chloramphenicol, are antagonistic to the fluoroquinolones.

Politics

Fluoroquinolones and group 4 cephalosporins are the main drugs used to treat serious Gram negative infections in people. The medical profession is not happy about their use in animals - **use them only for serious infections where nothing else is likely to work, preferably after a culture and sensitivity test**. This is a legal requirement for some products in food animals.

The future?

After a rush of new 8-methoxyfluoroquinolones onto the market, development of new drugs has paused, possibly because some of the newer drugs have caused serious cardiovascular side effects in people. Don't hold your breath for new veterinary drugs.

commonly misused drug

enrofloxacin

Nitroimidazoles

Nitroimidazoles include **metronidazole** (most commonly used in veterinary medicine), **tinidazole** (especially effective against *Giardia lamblia*), **dimetridazole** and **ornidazole**.

Mechanism of action

Nitroimidazoles cause a variety of injuries to DNA and DNA repair mechanisms in mammalian and bacterial cells. In anaerobic bacteria or microaerophilic organisms nitroimidazoles are thought to be reduced to toxic metabolites which damage DNA and DNA repair enzymes.

Spectrum of activity

Nitroimidazoles are active against a broad range of protozoa (eg *Giardia*, *Trichomonas*), all anaerobic cocci (Gram negative activity > Gram positive), Gram negative anaerobic bacilli, and Grain positive spore forming anaerobic bacilli. Metronidazole is usually used as a broad spectrum anti-anaerobe drug, particularly for *Bacteroides*, *Clostridia* and *Helicobacter*. It is not active against *Actinomyces*. Dimetridazole is commonly used against *B. hyodysenteriae*.

Resistance

Resistance is rare, but has been reported in swine dysentery treated with dimetridazole. This may be because anaerobes are not often cultured in veterinary medicine: *H. pylori* has suddenly become very resistant to metronidazole in people in the last two years (Auckland is much worse than the South Island!) This has followed the discovery that most gastric ulcers in people are caused by *H. pylori* and GPs starting to culture this organism (and using lots of metronidazole to treat it).

Cross resistance among the nitroimidazoles is probably complete.

Toxicity

A wide variety of toxic signs have been reported (nausea and vomiting or rashes are commonest), but toxicity is rare. Nitroimidazoles are not recommended in the presence of CNS disease or blood dyscrasias.

Metronidazole is reported to cause neurological side effects, such as loss of balance, head tilt, ataxia, nystagmus, disorientation, tremors and seizures. These effects may be due to overdosage or in some animals due to a decreased ability to metabolise the compound.

Acute pancreatic necrosis after metronidazole has been reported in humans (twice). It causes nausea and vomiting in the presence of alcohol, but this should not be a problem in animals!

Politics

Because they work by damaging DNA, nitroimidazoles are potentially carcinogenic and are banned for use in food animals in Europe and the USA, although they are still widely used in people there. This can cause problems with horses, which are officially considered food animals, even in NZ. (The unofficial solution to this problem is to use a six month withholding period.) Nitroimidazoles are important drugs for protozoal infections in people and the medical profession are not happy about pigs getting them by the ton.

Pharmacokinetics

Metronidazole is rapidly and completely absorbed after oral administration. Its bioavailability in monogastric animals approaches 100%. It is about 10% plasma protein bound. Metronidazole penetrates most tissues, excretions and secretions, including seminal fluid, vaginal secretions and milk.

Extensive hepatic metabolism occurs, and parent drug and a variety of inactive metabolites are excreted in the urine.

Pharmaceutical considerations

Metronidazole is available both for parenteral and oral use. The tablets taste revolting, and may be rejected by cats.

Use

Anaerobic infections in all species; gingivitis in dogs and cats. Dimetridazole is used for swine dysentery.

Metronidazole also has some immunosuppressive effect and is occasionaly used in desperation as an immunosuppressive, when all else has failed.

Human use

Anaerobic infections, amoebiasis, giardiasis, *Helicobacter* induced gastric ulcers.

The future?

Nitroimidazopyrans are closely related drugs being investigated for TB in man.

commonly used drugs

metronidazole

Nitrofurans

Nitrofurazone, **nitrofurantoin** and **furazolidone** are sometimes (rarely) used. They inhibit a variety of bacterial cell enzymes, but the actual mechanism of bacterial cytotoxicity is probably non-specific damage to DNA. This makes them suspect carcinogens and they are banned in food animals in Europe. They will probably be banned in food animals here soon, too.

Nitrofurans are active against many Gram negative and most Gram positive bacteria, including *Staphs*, *Streps*, *Corynebacterium*, coliforms, plus *Mycoplasma* spp and some protozoa. Resistance is by chromosomal mutation. Plasmid mediated resistance occurs but is rare. *Pseudomonas* and most *Proteus*, *Enterobacter* and *Klebsiella* are resistant.

Nitrofurantoin, the only systemically used member of this class, may cause vomiting and diarrhoea, and stains the urine brown. A variety of other systemic, idiosyncratic and hypersensitivity reactions have been reported including blood dyscrasias, hepatotoxicity and pulmonary infiltration.

Nitrofurantoin at recommended doses is absorbed rapidly after oral administration. It does not achieve therapeutic concentrations in the plasma because of very rapid renal excretion. Effective concentrations are achieved in the urine, and it is mainly used for urinary tract infections in dogs and cats, usually after inappropriate treatment has induced an infection resistant to more common drugs. Do not use in renal failure.

Nitrofurantoin is an acid with a pKa of 7.2 and is most active in acid urine, but solubility declines rapidly below pH 5.

Nitrofurantoin is used as tablets (human). Nitrofurazone is used as an antibacterial ointment (in combination with other drugs). Furazolidone is used as a feed additive in pigs and poultry to stop *E. coli* / *Salmonella* scours - do not use with dinitro.

Novobiocin

Novobiocin is an antiquated drug related to coumarin, which has not been used in people for many years because of the high incidence of side effects.

Novobiocin binds to bacterial DNA gyrase and inhibits DNA repair and transcription. The binding site is on a different subunit of the enzyme from that of the fluoroquinolones.

Novobiocin is mainly useful against *Staphs*. *Streps* are less sensitive, and enterococci and most coliforms are usually resistant, although it may be useful against some strains of *Proteus*. It may be synergistic with penicillin. It is also used in combination with sulphanilamide as a treatment for coccidia in poultry. Resistance develops quickly.

Novobiocin often causes vomiting and diarrhoea, blood dyscrasias, and occasionally skin rashes. It is very good at producing allergic reactions in people. It is a substrate for the renal organic anion transporter, which blocks secretion of other drugs and results in high renal concentrations.

Novobiocin is an acidic drug which should not be given with basic drugs such as the macrolides. Novobiocin is available mixed with tetracycline and dexamethasone for dogs and cats, and for formulation with feed or drinking water. Intramammary preparations are available overseas.

1 IU novobiocin = 1µg

Rifamycins

Rifampicin (rifampin USAN) is a complex macrocyclic antibiotic sometimes used in horses. It inhibits bacterial DNA-dependant RNA-polymerase in bacterial but not mammalian cells. Similar drugs such as rifabutin are also available overseas.

Rifampicin is a very broad spectrum bactericidal antibiotic which has limited usefulness because of very rapidly developed resistance - probably a one step mutation modifying DNA-dependant RNA-polymerase. Its most useful applications are in the treatment of tuberculosis and leprosy (in man), and the treatment of rhodococcal pneumonia in foals in combination with erythromycin. (Resistance to the combination develops much more slowly). It can be useful against *Staphs* in the short term, but must be given with another drug to slow development of resistance.

Rifampicin causes body excretions secretions to turn orange. It can cause rashes, and will cause mild alterations to liver enzymes. It is contraindicated in pregnant animals and in those with hepatic injury. The combination with erythromycin can cause fever.

Rifampicin is lipid soluble, and 75 - 90% plasma protein bound. It is well absorbed after oral administration. Rifampicin is distributed to most tissues with good penetration into the CNS and body cavities. Rifampicin is useful for

treatment of infections caused by intracellular bacteria.

Rifampicin is extensively metabolised by deacetylation in the liver (this metabolite also has antibacterial activity). Hepatic failure causes decreased clearance and accumulation.

Rifampicin should be reserved for treatment of TB in people. Its only indication in animals is for rhodococcal pneumonia in foals in combination with erythromycin, but even here, azithromycin (a macrolide) on its own may be better.

Rifamycins have been advocated for *Staph* mastitis since they usually penetrate tissues very well. Rifaximin is licensed for this in Italy, but it is one of the few rifamycins which is unable to penetrate tissues. Irresponsible use of these drugs in this way is likely to increase resistance in human pathogens, particularly TB, for which rifampicin is the first line treatment.

Other antibacterials

Hexamine (methenamine USAN) does not fit into any classification system so it is stuck in here at the end. It is sometimes called a urinary antiseptic. It is a complex amine which is excreted into the urine and broken down in acid urine to formalin, which kills any bacteria present. There is no resistance as such, but bacteria which alkalinise the urine stop the formation of the formalin. Still available in NZ (for people) but not used much (as an antibiotic at any rate - it is used as a fuel for camping stoves and in a wide range of industrial applications).

Triclosan is an old drug traditionally used as an antiseptic mouthwash. It has recently been discovered to act specifically against bacterial fatty acid synthesis and is being reinvestigated. It is effective against most Gram positive and Gram negative bacteria except *Pseudomonas*. It is also active against some fungi and protozoa. It is being investigated for malaria in man.

Quinoxalines such as **carbadox** (still used here) and olaquindox (no longer licensed) are mainly G- drugs previously used for growth promotion in pigs, now used to treat scours and prevent swine dysentery. These have been in use since before science was involved in drug licensing and very little is known about them except that they are potentially carcinogenic.

Heavy metals have antibacterial properties. **Silver** is the only one used therapeutically (usually in combination with sulphadiazine), copper and arsenic are used as growth promoters (qv). Oral colloidal silver was used as an antibacterial before antibiotics were discovered, but is not very effective in any infection. It has recently enjoyed a resurgence of popularity as a "natural" medicine. Overdose can irreversibly turn people's skin a blue gray colour - no information in animals.

Ionophores

Ionophores are another family of antibiotics produced by various species of *Streptomyces*. They are highly lipophilic monocarboxylic acids that are toxic to many bacteria, protozoa, fungi and higher organisms. There are a number of ionophores licensed for use in NZ (**lasalocid**, **maduramicin**, **monensin**, **narasin**, **salinomycin**, **semduramicin**). These are mostly fed in large quantities to chickens - vets are usually not involved.

Mechanism

The exterior of their molecules are hydrophobic, and the interior hydrophilic, being able to bind one (uniporters) or more (antiporters) cations. Their lipophilic nature allows them to readily penetrate cell membranes and act as a pore, allowing uncontrolled influx and/or efflux of selected ions, such as potassium and sodium. This uncontrolled ion flow interferes with the osmotic control mechanisms in cells, often leading to cell death. The different drugs transport different ions across the cell membrane: monensin - mainly Na^{+}; lasalocid - Ca^{++} and Mg^{++}, and to a lesser extent, K^{+}; salinomycin and narasin - mainly K^{+}.

Spectrum

Protozoa, mainly *Eimeria* spp.in animals, but also *Plasmodium* (malaria).

The susceptibility of Gram positive bacteria to ionophores varies according to bacterial cell wall structure. The structure of the cell envelope of Gram negative bacteria appears to influence susceptibility to ionophores through differences in ionophore binding and permeability. They have some effect against Gram positives, importantly *Cl perfringens*, and *Mycoplasma*, but most Gram negatives are resistant (ionophores do not reach their cell membranes).

B hyodysenteriae and *Lawsonia intracellularis* in pigs can be controlled clinically with ionophores. Monensin has been effecitive against an *Enterococcus*-like organism in trout.

The polyene antifungals nysatin and amphoteracin B are also ionophores.

Resistance

Organisms which produce ionophores have efflux pumps to get rid of the drugs, but the mechanism of resistance in pathogens is unknown.

Increased resistance to ionophores has been reported for *Staphs* in pigs and cattle and for enterococci in chickens and pigs. It has also been reported in the rumen bacterium, *Prevotella (Bacteroides) ruminicola* M384, which appeared to have arisen from chromosomal mutation not plasmid transfer, possibly resulting in decreased porosity of the outer membrane.

There appears to be no development of resistance in *Clostridia*.

The effects of the drugs are markedly influenced by the growth media, which adds uncertainty to reports of resistance.

Cross-resistance to other ionophores can occur, but resistance is not complete. Anecdotal evidence of resistance in chickens in NZ is emerging.

Toxicity

Monensin, and probably the other ionophores, is very toxic in low concentration for horses and dogs and in high concentration for cattle (myocardial degeneration). They are also very toxic to people and are not used in this species.

LD50s mg/kg	
cattle	22 - 80
horses	**1 - 2**
sheep	12
pigs	16
dog	10 - 20 (bitches lower)
chicken	200

Turkeys, Guinea fowl and Japanese quail are more susceptible than chickens.

Use

Monensin is by far the most widely used, mainly as a coccidiostat. Ionophores are primarily used in broilers, but also in layer replacements, goats, sheep and cattle for prophylactic control of coccidiosis caused by *Eimeria* spp. They may also have the useful side effect of preventing necrotic enteritis (*Cl perfringens*). They are also used to control swine dysentry and proliferative enteropathy in pigs. Salinomycin is also licensed as a growth promoter for pigs and beef cattle. Monensin is licensed for controlling bloat and ketosis as well as improving food conversion efficiency in cattle.

The improved feed efficiency effects in ruminants is due in part to a increase in the proportion of Gram negative to Gram positive bacteria. However, ionophores also appear to affect Gram negative bacteria, which may either be sensitive at concentrations likely *in vivo* and subsequently become resistant, or they may be able to grow but the presence of the ionophore causes altered metabolism. The net result is an increase in the proportion of propionate to acetate, and decrease in rumen ammonia, probably as a result of reduced hydrolysis of peptides, along with less proteolysis and deamination of amino acids in the rumen.

Bloat is a major health issue for grazing cattle, and coccidiosis of major concern to monogastric animals and neonatal ruminants. The effects of coccidiosis are debilitating and can be fatal, either directly or through increased susceptibility to other diseases such as necrotic enteritis, caused by *Clostridium*

perfringens, in poultry.

Other anti-bloat treatments are available, however, none are suitable for extensively grazed animals. The effect of monensin of reducing methane production and emission by ruminants, a major contributor to the greenhouse effect, could be considered beneficial to the environment.

Human use

Not used in people because of toxicity, but antimalarial use is a possibility in the future.

Interactions

Monensin reduces the uptake of macrolides into macrophages *in vitro*. Ionophores and tiamulin interact to severely retard growth in pigs.

commonly used drugs

monensin

Antibiotics - the future?

Bacterial fatty acid synthesis is starting to be targetted - mammals get their fatty acids from food so shoulc not be affected by these drugs.

The genome of many major pathogens is in the process of being sequenced. This is likely to lead to a variety of new approaches to killing bacteria or stopping them from infecting animals. Genes which code for resistance will be high on the hit list, or even the processes which allow bacteria to mutate happily without killing themselves in the process. Expect plenty of new antibiotics and other drugs targeted specifically at processes which only occur in pathogens. Also expect heavy pressure to prevent their use in animals. On a more optimistic note, many of the drugs which interfere with DNA transcription will be potential carcinogens; if they are rejected from human medicine for this reason, they may make it into veterinary medicine, although probably only for small animals.

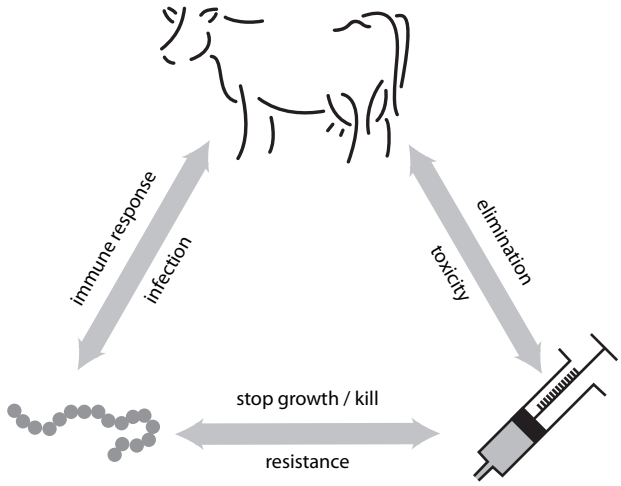
Further reading

Walsh, C. 2003, Where will new antibiotics come from? Nature Reviews: Microbiology, 1, 65 - 70

group	drugs	spectrum
penicillins	benzyl penicillin	G+, anaer, (G-)
	ampicillin, amoxycillin	G+, G-, anaer,
	co-amoxyclav	ß-l Staphs, G+, G-, anaer
	cloxacillin	ß-l Staphs, G+, anaer
cephalosporins	G1 - cephalexin	ß-l Staphs, G+, anaer, (G-)
	G2 - cefuroxime	G- (G+)
	G3 - ceftiofur	G-
bacitracin		G+, ß-l Staphs
polymixins		
tetracyclines	oxytetracycline, doxyclycline	all - but variable resistance
chloramphenicols	chloramphenicol, florfenicol	all - but variable resistance
macrolides & similar drugs	erythromycin, tylosin, licomycin, tiamulin	G+, ß-l Staphs, mycoplasma, spirochaetes
aminoglycosides	streptomycin, neomycin, gentamicin	G-
sulphonamides	sulphadiazine	G+, G-
potentiated sulphonamides	co-trimazine, co-trimoxazole	ß-l Staphs, G+, G-, anaer
fluoroquinolones	enrofloxacin	G-, (ß-l Staphs, some G+)
nitrofurans	nitrofurantoin	
nitroimidazoles	metronidazole	anaer
rifamycins	rifampicin	G+, ß-l Staphs
odds and sods	novobiocin	ß-l Staphs

Summary of antibiotics.

Therapeutic principles



The chemotherapeutic triangle

When antimicrobial drugs are administered to an animal (the host) infected with a pathogenic micro-organism, there is a triangular interaction between the the host, the micro-organism and the antimicrobial drug. These interactions must be considered when formulating a rational protocol for antibiotic use.

Host responses to antibiotics include:

- no effect
- allergic responses
- tissue drug residue deposition
- toxicity
- drug interactions with other therapy

Bacterial responses to antibiotics include:

- death of the micro-organism
- slowing or stopping of bacterial replication
- development of resistance
- super-infection

Success of antimicrobial therapy depends on achieving one of the two desirable responses while keeping undesirable effects to a minimum. Remember, the underlying principle of all drug use which was initially stated by Hippocrates (460-377 BC): "*Primum non nocare*." You must balance the risk of undesirable effects against the probability of benefits.

Drug selection process

For any antibiotic to work, the bacteria must be susceptible to the drug, and the drug must get to where the bacteria are. You should also consider the chances of clinically significant resistance developing, either in the animal(s) or environment / owner. There are also a number of other desirable factors. Follow the process below.

1. **Make a diagnosis**. Any treatment in the absence of a diagnosis is irrational. Therefore, before selecting an antimicrobial drug as (part of) a treatment, an attempt must be made to confirm that an infection exists.

2. **Identify the** (class of) **bacterium** causing, or likely to be causing the infection. A sample, smear and Gram stain is useful to help with this. In the practical clinical situation, it is not always possible to sample, smear, identify and culture the causative bacterium. You may have to rely on knowledge of the incidence of bacterial disease in your practice, and on the patterns of disease caused by commonly pathogens. This allows an empirical choice of antimicrobial. (A word of warning: charts which are to be found in text books showing incidence of bacterial diseases should be used as a guide only. Major differences occur in host species and between countries.) It is best to isolate, culture and test the resistance of the infective organism to available drugs. The infective microorganism must be sensitive to the drug chosen.

3. Consider **pharmacokinetics**. The drug must come into contact with the bacteria, ie, it must be adequately distributed to the infected tissue and it must be soluble in the milieu of the infected tissue matrix. The drug must be able to reach high enough concentrations at the site of the infection to affect the bacteria, ie, the drug must achieve a concentration greater than the MIC for the causative bacteria at the site of the infection (ideally 4 - 5 times the MIC should be achieved in the plasma). The drug must be present for sufficient length of time at the site of the infection but must not reside in tissues excessively (especially in food producing animals). To achieve all this, the correct dose and frequency must be chosen.

4. Consider **resistance**. It is better to choose a drug for which resistance is slower or less likely to develop. A narrow spectrum drug will exert less selection pressure on non target organisms. Use drugs which are less likely to produce clinically significant resistance in the animal, owner or environment; eg, if a penicillin is likely to work as well as a cephalosporin, use the penicillin.

5. Consider **host factors**

Species: what drugs are licensed?

Is this a food producing animal? - withholding times!

Are there any *other restrictions* (racing animals)?

What *routes of administration* are practical and are there appropriate formulations?

Is the animal *pregnant* / *lactating*?

Age: are there special toxicity or dose rate considerations?

Body weight: are there special toxicity or practical dosing considerations?

Is the animal *adequately hydrated* and do the animal's kidneys work?

Is there evidence of *biliary obstruction*?

Is the animal *immunocompetant*?

6. Consider the **mechanism of action** of the antimicrobial drug of choice. Until recently it was thought better to choose a drug which is nominally bactericidal over one which is merely bacteriostatic. However, it is now clear that little information exists as to whether a particular antimicrobial drug is bactericidal or bacteriostatic against a particular infective organism at the concentration reached at the site of infection. It is more important to consider whether or not the drug is likely to penetrate well to the site of infection, and whether it will be active in that environment. The distinction between bacteriostatic and bactericidal drugs is probably only important in immunocompromised animals.

7. The probable **toxic effects** of the chosen drug should be considered. The frequency of immune mediated reactions to the antimicrobial drug formulation should be considered.

8. **Interactions** between the chosen drug and any other present or potential medications should be anticipated.

9 The propensity for the drug to initiate **super-infections** should be considered, especially in some species (eg, the horse, guinea pig).

10. The ease of **administration**, and the pain and / or stress caused by the administration of the chosen drug should be considered. These factors are important both from client compliance and animal ethical view points. The pain caused by deep intramuscular injections of certain antibiotic preparations is probably overlooked as a major cause of continuing debilitation.

11. The **cost** of the chosen drug should be considered.

12. **Supportive treatment** may make a big difference to the outcome.

Finally, assess the risk / benefit ratio! (but see also the guidelines below).

13. **Monitor** the effects of the drug - reduction in fever etc - to check that your selection was suitable.

Common problems

Factors under control of the veterinarian:

The most common reason for misuse of antibiotics is a failure to make a diagnosis. This often derives from an invalid assumption that an elevated temperature or fever means an infection. The diagnosis "fever of unknown origin" is not in itself sufficient justification for administration of antimicrobial drugs.

Another common error is to fail to identify the infective organism, even empirically. This leads to the frequent prescription of broad spectrum antibiotics. Broad spectrum antibiotics are more likely than those with a narrower spectrum to induce super-infection and bacterial resistance. From the legal point of view, the medical record should indicate the reason for the choice of drug. Habitual use of a broad spectrum antimicrobial drug indicates a low (and unacceptable) standard of diagnosis.

Isolation of the wrong organism occurs frequently. Therefore, laboratory reports should be considered carefully, not blindly acted upon. It is necessary to reconsider the method of sampling (aerobic vs anaerobic), and the suspected agent (bacteria, mycoplasma, viruses).

Inappropriate choice of antimicrobial drug is a leading cause of failure of therapy. Assuming an organism has been identified, there really is no excuse for this. Often this error occurs because of a lack of knowledge. Does the drug of choice cross the blood/brain barrier? Does it have access to the prostate? Is it excreted in an active form in the urine? etc...

Inappropriate dose schedules (too little, too infrequently, not for long enough), and failure of client compliance in dosing are frequent causes for failure of antimicrobial therapy.

Failure will often result from not providing adequate ancillary therapy, eg, drainage for an abscess.

Factors not (necessarily) under control of the veterinary surgeon

Bacterial resistance to the chosen antimicrobial drug occurs frequently in some clinical settings. In general, resistance patterns cannot be predicted. Bacterial resistance to the chosen antimicrobial drug can also develop during the course of therapy.

Mixed infections can result in disease in which it is difficult to adequately identify all active bacteria.

Lack of correlation between *in vitro* tests and *in vivo* sensitivity occurs frequently. A knowledge of pharmacokinetics and pathology should allow this to be predicted in most cases.

Occasionally, treatment has to be stopped because of side effects.

"Antimicrobial sensitivity" testing

Samples for isolation and culture of bacteria from infected tissues can be very useful in selection of appropriate drugs since different bacterial species have different patterns of antimicrobial sensitivity. However, not all resistance patterns can be predicted. Therefore, testing the sensitivity of bacterial isolates to available drugs should be carried out where practicable.

If an organism is resistant to an antimicrobial drug *in vitro*, then it will almost certainly be resistant to the same drug *in vivo* (assuming it has been properly cultured on the correct medium). However, if an antimicrobial drug is effective *in vitro*, it is not necessarily effective *in vivo*. Hence, laboratory testing is really resistance testing and not sensitivity testing.

The results of Kirby-Bauer sensitivity tests can be misleading. The diffusion of the drug through the culture media may be impeded or enhanced relative to other drugs, leading to altered expectations of its efficacy. The media may contain factors which allow the bacteria to avoid toxicity, e.g. para-aminobenzoic (PABA) will antagonise the effect of sulphonamide antimicrobials. Different labs use different techniques, although the American NCCLS protocols are probably commonest. MIC data is much more useful than merely "R" or "S".

The presence of antibiotic in samples taken from animals already treated with an antibiotic may prevent bacterial growth *in vitro*, despite their failure to do so *in vivo*. So take the samples for culture and sensitivity testing **before** you give the drug. If empirical therapy has been started and has failed, then all antimicrobial drugs should be withdrawn 2

to 3 days before samples are taken for culture.

From the practical point of view, it is important to request the testing for sensitivity to drugs which are available for use by the route necessary to reach the site of infection.

Prophylaxis

Rational use of antimicrobial drugs for prevention of infectious disease is limited to very few applications: either where there is a predictable high risk of infection which cannot be reduced in any other way, eg, immunocompromised patients, or a few sick animals in a herd which cannot be separated; or where the consequences of infection would be disastrous, eg, some orthopaedic implants.

In small animal medicine, prophylactic antimicrobial therapy is only rational for severely immunocompromised patients, such as those with diabetes mellitus, those with myelogenous leukaemia, or those on immunosuppressive chemotherapy. In procedures such as catheter placement there is no justification for the use of antimicrobial drugs. Aseptic technique when placing and regular replacement of intravenous catheters should be sufficient to prevent infections.

In food animal medicine, antibiotics are frequently overused to prevent infections. They are not a susbtitute for good hygiene. See guidelines below.

The use of antibiotics in surgical procedures should be limited to cases where bacteraemia is likely to be produced and the animal is immunocompromised or has an implant of some sort (eg, an orthopaedic plate). **Antibiotics are not a substitute for aseptic technique!**

Guidelines for antimicrobial prophylaxis in surgery

Use penicillins or cephalosporins, iv if possible. They are bactericidal, achieve peak tissue levels rapidly (approximately 20 - 40 mins, so give the drug half an hour before surgery), and are relatively non toxic. The more strongly protein bound drugs in these classes (oxacillin, nafcillin) do not penetrate fibrin as well as the less strongly protein bound (ampicillin, penicillin). Use intermittent bolus dosing at half the normal dosing intervals (about every 2 hours for iv ß-lactams). This regime produces approximately 2 - 4 times higher tissue concentrations than does iv infusion. Continue therapy throughout surgery but there is no value in prophylactic treatment afterwards.

Cephazolin sodium 20mg/kg iv every 2 hours gives broad spectrum cover.

Review

Moore, A.H. 1996 Rational use of antibiotics in surgery. *The Veterinary Annual*, 36, 57 - 66

before using a drug ask:

- **does it kill the bacteria?**
- **does it get to where the bacteria are?**
- **is clinically significant resistance likely to develop?**
  - **in the animal?**
  - **in the herd or contacts?**
  - **in the environment or people?**

Guidelines on the use of antimicrobials

These guidelines were produced by the BVA and published in the Veterinary Record of 14th November 1998, pp565 - 566. The NZVA is working on something similar, to be published some time soon (?!), as well as a more detailed set of guidelines similar to the infection of systems bit later on in this study guide. Check the website `http://www.vets.org.nz`

Following guidelines such as these is a good way of making sure that you are using these drugs responsibly. The section on regulatory concerns is not directly relevant to NZ, but gives some idea of the shape of things to come!

These guidelines are intended to act as an adjunct to clinical judgment. It may not be possible for every consideration to be observed in every case, but they should always form part of an automatic checklist when deciding on an antimicrobial use regime

Introduction

(1) The use of antimicrobial agents provides an effective method for the control and treatment of infectious or contagious diseases caused by bacteria and certain other micro-organisms. Their application in veterinary.practice since the 1950s has assisted.in ensuring the health of livestock and.companion animals. Antimicrobial use has. also enabled the production of meat and.milk products which are unlikely to present disease problems for the consumer or those concerned with their production. Antimicrobial use is also justifiable on animal welfare grounds ('freedom' to receive treatment for disease is incorporated in the Welfare Codes).

(2) It must be remembered at all times that widespread use of antimicrobials is not a substitute for efficient management or good husbandry practice.

Principles of antimicrobial use

(3) The appropriate selection of antimicrobials in practice is a critical decision and should be based on:

(a) accurate diagnosis;

(b) known or predictable sensitivities (sensitivity testing);

(c) known pharmacokinetics/tissue distribution to ensure the selected therapeutic reaches the site of infection;

(d) known status of immunocompetence.

Routine considerations

(4) Antimicrobial agents should only be used when it is known or suspected that an infectious agent is present which will be susceptible to such therapy.

(5) When antimicrobial agents are used, every effort should be made to determine the origin of the problem and to ascertain the most effective treatment.

(6) While therapy may need to be initiated before the results of diagnostic or sensitivity tests are known, it will need to be reassessed as test results become available. In such circumstances, before the results are known, decisions as to the choice of antimicrobial will need to be made:

(a) in the light of what has previously been effective in similar types of problems;

and

(b) on any knowledge of previous antimicrobial efficacy on the premises.

(7) Infectious disease should be treated with the antimicrobial found, on appropriate testing, to be most efficacious and also based on the previous history of effective antimicrobial use on the premises.

(8) Careful calculation of dose is always important, but in particular if an extra-label use of a product is being considered. In such cases, caution needs to be exercised regarding meat and milk withholding periods.

(9) The efficacy of all disease treatments should be monitored and, if part of the treatment regime was undertaken by the livestock or pet owner, a check should be made to ensure that they have understood fully the instructions on dosage and duration of any antimicrobial use. Quantities of antimicrobials left with the animal owner should correctly reflect the needs, to avoid an over-supply.

(10) Antimicrobial usage should always be part of, and not a replacement for, an integrated disease control programme. Such a programme is likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination, etc.

(11) Continued antimicrobial use in such control programmes should be regularly assessed as to effectiveness and whether their use can be reduced or stopped.

(12) Protocols should be agreed between the veterinary surgeon and the client as to when veterinary involvement is required in on-going disease conditions. These protocols must be regularly and frequently reviewed and updated.

(13) Protocols should be agreed and documented for treatment of all endemic conditions on the farm or other livestock-rearing or production premises. These protocols must be regularly reviewed and updated.

Dosage strategy recommendations

(14) In order to minimise the likelihood of broad antimicrobial resistance developing, it is recommended that where an appropriate narrow spectrum agent is made available it should be selected in preference to a broad spectrum agent, which will exert a greater selection pressure on commensal bacteria.

(15) It is recommended that optimal therapeutic dosage strategies be used and that all efforts be made to avoid administration of sub therapeutic dosages, which can lead to a lack of efficacy (and, in some specific cases, such as fluoroquinolones and erythromycin, has been shown to induce resistance). Dosage recommendations as laid down in the relevant data sheet should always be followed.

(16) Should there be recurrence of disease following successful treatment (and control) of an outbreak, it will need to be investigated thoroughly to ascertain why this has occurred and the most suitable therapy to be used.

(17) Use of antimicrobials for the prevention of disease can only be justified where it can be shown that a particular disease is present on the premises, or is likely to become so, and that strategic antimicrobial use will prevent clinical outbreaks of that disease.

(18) Antimicrobials need to be used with care to maintain their efficacy. If possible, look for alternative methods of disease control (vaccination) to reduce antimicrobial use.

Regulatory concerns

(19) Any use of antimicrobials outside normal data sheet recommendations (in accordance with the prescribing 'cascade') should be carefully justified and documented.

(20) Note must be made, and documented, of any adverse reactions which may be observed or a decline in efficacy of a previously effective antimicrobial.

(21) All antimicrobials in use must be used and stored correctly in the manner outlined in the BVA Code of Practice on Medicines. In accordance with statutory requirements, full records must be kept of all products used.

(22) Consideration must always be given to the health of the person administering the products. Any necessary warnings should be issued.

Stick to the guidelines!

If that's too difficult, there's a simplified version over the page.

BVA
British Veterinary Association

RESPONSIBLE USE OF ANTIMICROBIALS
IN VETERINARY PRACTICE: THE 8-POINT PLAN

1 Work with clients to avoid need for antimicrobials

- Integrated disease control programmes
- Animal Health and Welfare Planning
- Isolate infected animals wherever possible

2 Avoid inappropriate use

- For example, for uncomplicated viral infections
- Restrict use to ill or at-risk animals
- Advise clients on correct administration of products and completion of course
- Avoid underdosing

3 Choose the right drug for the right bug

- Identify likely target organisms and predict their susceptibility
- Create practice-based protocols for common infections based on clinical judgement and up to date knowledge
- Know how antimicrobials work and their pharmacodynamic properties
- Use antimicrobials with a spectrum as narrow as possible

4 Monitor antimicrobial sensitivity

- While clinical diagnosis is often the initial basis for treatment, microbiological sensitivity must be determined whenever possible so that a change of treatment can be implemented if necessary

5 Minimise prophylactic use

- Use only when animals are at risk and evidence that usage reduces morbidity and/or mortality
- Regularly assess prophylactic use and develop written protocols for when prophylactic medication considered appropriate
- Monitor antimicrobial sensitivity trends

6 Minimise use perioperatively

- Use only when necessary and supported by strict aseptic techniques alongside written practice guidelines

7 Record and justify deviations from protocols

- Be able to justify your choice of antimicrobial and dose
- Keep accurate records of treatment and outcome to help evaluate therapeutic regimens

8 Report suspected treatment failure to the VMD

- This may be the first indication of resistance
- Report through the Suspected Adverse Reaction Surveillance Scheme (SARSS)

SPECIAL NOTE

Fluoroquinolones and third-/fourth-generation cephalosporins:

- Reserve these antimicrobials for clinical conditions that respond poorly to other classes of antimicrobials and where antibiotic sensitivity has been carried out.
- Do not administer systemically to groups or flocks of animals except in very specific situations and special attention should be given to the risk of antimicrobial resistance as part of the benefit/risk assessment.
- Avoid off label use whenever possible

FOR FURTHER GUIDANCE VISIT

www.bva.co.uk

ANTIMICROBIALS ARE ESSENTIAL FOR THE TREATMENT AND PREVENTION OF INFECTIOUS AND ZOONOTIC DISEASES IN BOTH ANIMALS AND HUMANS

EVERY USE INCREASES THE RISK OF DEVELOPMENT OF MICROBIAL RESISTANCE

RESPONSIBLE USE OPTIMISES THERAPEUTIC EFFECTS WHILE MINIMISING RESISTANCE DEVELOPMENT

RESPONSIBLE USE — AS LITTLE AS POSSIBLE, AS MUCH AS NECESSARY

Infections of systems

"First guess" empirical antimicrobial therapy is often necessary both because of a client's financial restrictions and because of the need to begin treatment as a life-saving measure before the results of culture and sensitivity testing become available. However, if you expect the drug to work, an attempt must be made to identify the microorganism(s) involved and their likely antimicrobial resistances.

Two major considerations in large animal practice are cost and practicality. Although you should help the farmer consider the benefits of antimicrobial therapy on a basis of economic returns, you also have a legal and ethical responsibility to relieve animal suffering. It can be very difficult to reconcile these two roles.

You should also bear in mind public health and the chances of significant resistance developing. This involves having a basic understanding of which drugs are important in human medicine. If you use antibiotics which might increase resistance in serious Gram negative infections in people (eg, cephalosporins or fluoroquinolones), MRSA (eg, glycopeptides) or MDR TB (eg azithromycin), you must be prepared to justify your choice. A culture and sensitivity test showing nothing else is likely to work is probably the best justification. This is already a legal requirement in some cases.

Recommended reading

Cooper, BS (ed) Antimicrobial Prescribing Guidelines for Veterinarians, 2nd ed, Postgraduate Foundation, University of Sydney.

Although this book is Australian, a lot of it is just as relevant to NZ, particularly the cattle section.

before using a drug ask:

- **does it kill the bacteria?**
- **does it get to where the bacteria are?**
- **is clinically significant resistance likely to develop?**
  - **in the animal?**
  - **in the herd or contacts?**
  - **in the environment or people?**

impress this firmly into your brain!

Cardiovascular system

A complete work up is necessary to try to find the original focus of infection, eg, vegetative endocarditis, unless it is obvious, eg, umbilical infection in a neonate. This is necessary to make sure that the chosen drug gets to the site of the infection. Blood cultures are often negative as bacteraemia tends to be episodic. Multiple cultures may be necessary. Bacteraemia is thought to precede fever spikes.

Treatment must begin before bacterial isolation and identification, especially as it is often difficult to isolate the causative organism. Early, aggressive, broad spectrum anaerobic and aerobic treatment at high dose rates is recommended.

animal	disease	bacteria	first choice	second choice
dogs	septicaemia, endocarditis	*Staphs, Streps, E.coli*	gentamicin & amoxycillin	cephalexin
cats	infectious anaemia	*Haemobartonella felis*	doxycycline	azithromycin
pigs	erysipelas	*Erysipelothrix*	penicillin	co-trimazine
foals	septicaemia	coliforms, *Pseudomonas*	ceftiofur	gentamicin

Skin

Successful treatment of skin infections usually requires ancillary treatment for ectoparasites or inflammation. Many, if not most, cases of skin infection in dogs and cats are the result of atopy and antimicrobial drugs alone rarely work. This is especially true for suppurative otitis externa caused by bacteria such as *Pseudomonas* which rapidly develop resistance over the course of treatment. As the condition is likely to recurr, this makes subsequent treatment difficult. The atopy should be treated - consider prednisolone or cyclosporin. Non antibiotic treatment should be used for the otitis where possible: the ear should be cleaned and dried, and possibly acidified (with a proprietary acidic cleaning soltution or dilute vinegar) to discourage *Pseudomonas*. Remember to check if the ear drum is intact as many drugs are potentially toxic in the middle ear.

The commonest skin pathogen in dogs is *Staphylococcus intermedius*, usually coagulase positive, and frequently penicillinase producing. Narrow spectrum drugs are best. Superficial infections may be better treated with antiseptic washes (chlorhexidine or povidone iodine).

Gingivitis is common in cats and dogs. Most pathogens are Gram negatives or anaerobes with normal commensals being Gram positive. Chlorhexidine mouthwashes are useful before dentistry, gingivitis involving bone loss usually needs antibiotics.

Burns can be especially difficult to treat. Contamination with bacteria is almost guaranteed as burned skin is an ideal culture medium. There is no evidence that systemic antibiotics are of any value, unless bacteria have invaded systemically. Topical therapy aims to physically obstruct access to the underlying dermis for bacteria, and to reduce bacterial numbers with a bactericidal gel.

Politics

Development of resistance always needs to be considered when treating dogs with skin infections as treatment may have to be prolonged and there is good overseas evidence that the prevalence of resistant bacteria in dogs is increasing. Clinical trials of antibiotics for skin infections typically last for three or four weeks, so resistance development is rare in these.

A recent study from Denmark has shown that 46% of owners of dogs with deep pyoderma have the same strains of antibiotic resistant *Staph. intermedius* as their dogs. Think about the transfer of resistance to human staphs before treating the dog!

Methicillin resistant staphs have been found in dogs. There has only been one reported case in NZ so far, but it is getting more common overseas.

Fluoroquinolones can be very effective for skin infection in dogs, at least in the short term, but overseas data indicates that resistance in *Staph. intermedius* is developing, so fluoroquinolones are probably best reserved for cases where other drugs are unlikely to work.

animal	disease	bacteria	first choice	second choice
all	wounds	*Staphs, Streps, E.coli, Clostridia, Pasteurella*	co-amoxyclav	co-trimoxazole
cats	bites	anaerobes and *Pasteurella*	penicillin & drain	co-amoxyclav
all	burns	*Pseudomonas, Klebsiella, Proteus*, β-haemolytic *Streps, Staphs*	silver sulphadiazine	polymixin/neomycin/bacitracin
dogs	pyoderma	*Staph intermedius*	co-amoxyclav	cephalexin
dogs	otitis externa	*Malassezia*	clotrimazole	miconazole
dogs	otitis externa	*Staphs, E. coli, Proteus*	acidic cleaning solution	polymixin/neomycin/antifungal
dogs	otitis externa	*Pseudomonas*	flush & silver sulphadiazine	flush & enrofloxacin
dog & cat	gingivitis	mixed	metronidazole ± co-amoxyclav	metronidazole ± clindamycin

drug	Australia '98[1]	Spain '96[2]	France '96[3]	Denmark '95[4]	Canada '02[5]	USA '02[6]	USA '98[7]	Hungary '97[8]
penicillin	22		57 (1988)	50	25 - 40	38	36 - 41	
co-amoxyclav	100		99	100	50 - 90		100	98
cloxacillin (oxacillin)	96		(98)		20 - 90	(100)		50
1st G cephalosporins	98		98		82 - 100	100	78 - 93	98
tetracyclines	92	72	65	80	10 - 60	63	58 - 62	19
macrolides	84 - 90	44 - 72	72 - 77	76	10 - 70	73		58 - 62
trim / sulph	58	24	64	100	20 - 25	82	36 - 52	62
fluoroquinolones		71 - 97	95 - 98	100	50 - 95	100	86 - 96	98

Percentage of Staph intermedius *from dogs susceptible to various antibiotics* in vitro. *There are no published data for NZ.* [1]*Mueller et al., 1998, Aus Vet Practit,* ***28****, 10 - 12;* [2]*Piriz et al., 1996, J Vet Pharm Ther* ***19****, 118-23;* [3]*Pellerin et al., 1998, Comp Imm Micro & Inf Dis,* ***21****, 115 - 133;* [4]*Pedersen & Wegener, 1995, Acta Vet Scand,* ***36****, 335 - 342;* [5]*Hoekstra & Paulton, 2002, J App Micro,* ***93****, 406–413;* [6]*Peterson et al., 2002, J Am Anim Hosp Assoc,* ***38****, 407–413;* [7]*Cole et al., 1998, JAVMA,* ***212****, 534 - 538;* [8]*Kiss et al., 1997, JSAP,* ***38****, 51 - 56;*

Respiratory system

The upper respiratory tract is frequently infected with viral pathogens. Elimination of normal flora by antibiotics can make the disease better or worse. Therefore, although culture and isolation is complicated by an abundant commensal population, it is very important to make a diagnosis. Purulent discharge is not pathognomonic for bacterial infection. Antibiotics are probably not indicated in the majority of upper respiratory tract infections in any species.

Infections of the lower respiratory tract are relatively common. Usually the bacteria concerned are aerobes and approximately two thirds are G-. Except in the case of aspiration pneumonia, pure infections are common. Therefore, culture and sensitivity testing is usually successful and valuable.

Cattle and sheep live outdoors at grass in NZ which means that they avoid most of the respiratory diseases caused by intensive husbandry systems overseas (pigs and chickens are not so lucky). In cattle, these are generally lumped together as bovine respiratory disease complex. Extensive use of antibiotics overseas has resulting in a high prevalence of resistance: this is not the case in NZ. Because these infections often occur as outbreaks in a herd, cost is a major consideration in the choice of drug. Transtracheal washings (or post mortem samples) followed by smear culture and sensitivity may be necessary to find the cheapest effective drug. Remember milk and meat residues!

Antibiotics are not a substitute for good husbandry.

animal	disease	bacteria	first choice	second choice
cattle & sheep	pneumonia / BRD	*Pasteurella* ± others	penicillin	oxytetracycline
horse	pneumonia	*Streps*	penicillin	
foal	pneumonia	*Rhodococcus equii, Strep zooepidemicus*	erythromycin & rifampicin	azithromycin
horse	strangles	*Strep. equii*	penicillin	co-trimazine
dog & cat	pneumonia	*Pseudomonas, E. coli, Klebsiella*	gentamicin	enrofloxacin
dog & cat	pneumonia	*Streps & Staphs*	ampicillin	erythromycin
dog & cat	pneumonia	unknown	co-amoxyclav	co-trimazine
pigs	enzootic pneumonia	*Mycoplasma*	tylosin	oxytetracycline
pigs	pleuropneumonia	*Actinobacillus*	penicillin	oxytetracycline

Urinary tract

Firstly rehydrate the animal / encourage it to drink to produce an adequate urine output.

Uncomplicated cystitis in female dogs should probably be treated for 7 days, although there should be improvement in hours and clinical resolution in 3 days. A single large dose of antibiotic may be sufficient. In male dogs the prostate is usually involved and 4 - 5 weeks of treatment is usually required. If there is some predisposing factor, all that long courses of antibiotics do is to ensure that resistant bacteria develop. If there is not a dramatic improvement in three days, the animal should be thoroughly examined and the diagnosis confirmed. If you induce a multiresistant infection, you will have to resort to old drugs such as nitrofurantoin and hexamine, which are more likely to cause side effects.

The concentration and activity of an antimicrobial drug in the urine varies according to the pH of the urine. Although urinary pH can be altered to suit the preference of the chosen antimicrobial drug. It is more sensible to consider the activity / pH spectrum of the drugs available, and to choose a drug which is active in the conditions to be found. Remember, though, that as an infection is controlled, the pH of the urine may alter. Drugs with optimum activity in acidic urine are themselves acids or neutral: penicillins, tetracyclines, nitrofurantoin, hexamine. Drugs active in alkaline urine are themselves bases or neutral: erythromycin, aminoglycosides. Drugs relatively unaffected by pH: cephalosporins, sulphonamides, chloramphenicol, fluoroquinolones.

Many antimicrobial drugs are concentrated in the urine, particularly ß-lactams, so *in vitro* resistance does not necessarily indicate that the drug will not be effective *in vivo.* Ensure that sensitivity testing is carried out at concentrations of antimicrobial drugs relevant to urinary tract concentrations of drug *in vivo*.

Leptospiral nephritis is best prevented by vaccination. If streptomycin is used to treat it in food animals, remember that it has a **very** long meat withholding time.

animal	disease	bacteria	first choice	second choice
dogs & old cats	cystitis	*E.coli, Staphs, Streps, Proteus, Pseudomonas*	co- amoxyclav	co-trimazine
sows	cystitis / pyelonephritis	*Corynebacterium suis*	penicillin	co-trimazine
cattle	pyelonephritis	*Corynebacterium renale*	penicillin	co-trimazine
food animals	nephritis	*Leptospira*	streptomycin	oxytetracycline

Central nervous system

The drug chosen must be able to cross the blood brain barrier. Large molecules and highly protein bound drugs do not have access through a normal blood brain barrier, but during inflammation most drugs get in.

Most drugs are removed from the cerebrospinal fluid by active transport and therefore do not achieve concentrations in central nervous tissue which are equivalent to plasma drug concentration - give bigger doses than usual. Lipid soluble drugs achieve high concentrations (in general) in nervous tissue: sulphonamides, trimethoprim, enrofloxacin, metronidazole, chloramphenicol.

The intrathecal route for administration of antimicrobial drugs is occasionally used, but has significant toxicity problems. Most drugs are not isotonic or body pH and cause neuronal excitation - convulsions.

Listeriosis in ruminants must be treated aggressively to be successful, but this is rarely economic.

animal	disease	bacteria	first choice	second choice
dog & cat	meningitis	*Staphs, Pasteurella, Actinomyces, Nocardia*	co-amoxyclav	co-trimazine
pig	meningitis	*Strep suis*	penicillin	oxytetracycline
ruminants	meningitis	*Listeria monocytogenes*	amoxycillin Na	penicillin Na

Gut

Antimicrobial therapy is *NOT* indicated for routine treatment of undiagnosed or non specific acute or chronic gastrointestinal disease. Fluids should be used instead. The only specific indication for antimicrobial therapy is invasive bacterial infection, secondary to mucosal damage. This applies also to diseases such as salmonellosis and coliform diarrhoea. Prevention is better than cure!

Normal flora are affected by most antimicrobial drugs. Anaerobes predominate distal to the ileum, but are difficult to culture. Broad spectrum antibiotics play particular havoc with the rumen microbial population.

With the exception of potentiated sulphonamides and certain formulations of penicillin (not available in NZ), all oral antimicrobials are contraindicated in the adult horse since they can cause diarrhoea. Potentiated sulphonamides are used nevertheless.

Coccidial diseases are better prevented than cured -monensin (toxic to horses) and many other coccidiostats are available.

Peritonitis occurs after perforation of the bowel. The primary problem must be sorted out which usually means surgery. Flushing the peritoneal cavity is essential. Vigorous antimicrobial therapy is required using a broad spectrum combination including anaerobic cover.

Mass medication in sheep has been tried in an attempt to control *Salmonella* Brandenburg: it did not prevent abortions. However, sheep and cattle continue to excrete *Salmonellae* for long periods, so there is a (weak and unproven) argument for treatment to prevent this shedding. In people, antibiotic treatment prolongs shedding of *Salmonella. Salmonella* infections in other species should not be treated with antibiotics unless a bacteraemia develops. Remember that *Salmonella* infections are zoonotic and potentially lethal in children and old people.

Politics

Oral antibiotics were used as growth promoters for many years (and still are in some countries). This use has been shown to lead to antibiotic resistant pathogens and commensals in the gut and has given antibiotic use in animals a bad name. Nasty pathogens such as *E. coli* O157 and *Salmonella* Typhimurium DT104 are not a problem in NZ (yet), but the situation in the UK shows what could happen. *Enterococci* are usually commensals, but can cause disease: vancomycin resistant *Enterococci* have been found in chickens and people in NZ.

Think carefully about the effects on the gut flora of **any** antibiotic you give!

animal	disease	bacteria	first choice	second choice
calves	diphtheria	*F. necrophorum*	penicillin	sulphonamide
most species	coccidiosis	mainly *Eimeria*	sulphadimidine	amprolium
pigs	swine dysentery	*B. hyodysenteriae*	tiamulin	tylosin
neonates	invasion of mucosa and enteritis	*E. coli*	co-trimazine	apramycin
chickens	necrotic enteritis	*Cl. perfringens*	bacitracin	avilamycin
horse	peritonitis	gut flora	penicillin & gentamicin & metronidazole	
cattle	peritonitis	gut flora	co-trimazine	oxytetracycline

Eye

Most infections are superficial and most drugs will easily get to where the bacteria are. Chloramphenicol was widely used because it has excellent ability to penetrate both chambers of the globe, but it is banned in food producing animals (florfenicol can be used instead). However, infections of the deeper structures will probably require systemic antibiotics.

Most antibiotics are applied as drops or ointments. Subconjuctival injections can be made to prolong a drug's action. These routes can lead to significant systemic absorption and thus residues in food animals - remember withholding times. Powders should never be applied to the eye.

animal	disease	bacteria	first choice	second choice
dogs	superficial keratitis	*Staphs, Streps*, coliforms	gentamicin	neomycin/polymixin/ bacitracin
horses	conjunctivitis	*Staphs, Streps*, coliforms	gentamicin	neomycin/polymixin/ bacitracin
cattle, sheep, goats	pink eye	*Moraxella bovis*	cloxacillin	oxytetracycline

Reproductive tract

Penetration of the drug to the site of the infection is a major problem. Normal prostatic fluid has a pH of about 6.4, so weak bases penetrate best. This is important in chronic prostatitis - in acute cases the barrier is usually broken down by inflammation. Castration or an antiandrogen such as delmadinone are usual adjuncts to antibiotics for prostatitis.

Antibiotics are used to treat both acute and chronic uterine infections in cattle. However, for acute metritis the current trend is toward inducing oestrus with prostaglandins and away from antimicrobial therapy. Chronic metritis in all species is treated by uterine infusion, or systemic antimicrobials if there is evidence of deep tissue or systemic infections. Local intrauterine infusions are used to treat acute and chronic infections, unless there is evidence of deep tissue or systemic infections. A significant amount of drug can be absorbed - remember withholding times!

In the acute phase, care must be made to differentiate simple contamination from true infections. Contamination is not treated with antimicrobial drugs.

Although still common in clinical practice, the routine use of intrauterine pessaries (usually oxytetracycline), especially as prophylactic therapy, has fallen into disfavour.

animal	disease	bacteria	first choice	second choice
dogs	prostatitis	*E coli, Pseudomonas, Staphs, Streps, Proteus*	co-trimazine	macrolide / fluoroquinolone
dogs	pyometra	sterile / ditto	surgery ± co-amoxyclav	
cattle	metritis	*A. pyogenes, F. necrophorum*	induce oestrus / prostaglandins	oxytetracycline iu
mare	metritis	*Streps, Pseudomonas, Klebsiella, Aerobacter*	penicillin ± gentamicin	

Bone and joints

Osteomyelitis requires aggressive treatment with antibiotics. Although most antibiotics should reach adequate concentrations in bone when dosed appropriately, adequate blood supply to the site is also necessary. Areas of necrotic bone or sequestra will not heal without surgery. Parenteral antibiotics are indicated if a bacteraemia or septicaemia are present, otherwise oral antibiotics for 4 - 6 weeks should be used. Cephalosporins or co-amoxyclav are usually used. Tetracyclines should not be used as they bind to calcium in the bone and their activity is reduced.

Discospondylitis usually responds readily to antibiotics. If good improvement is not seen after five days, the animal should be re-evaluated.

Infected arthritides are common in foals. They can be caused by a variety of organisms. Culture and sensitivity is necessary. Treatment usually involves arthrotomy and flushing, as well as antibiotics.

Foot rot should be prevented or treated before it gets to the stage of osteomyelitis.

animal	disease	bacteria	first choice	second choice
dogs	osteomyelitis	usually *Staphs*	co-amoxyclav	lincomycin & aminoglycoside
foals	arthritis	a variety	gentamicin	
horses	arthritis	a variety	penicillin & gentamicin	
pigs	arthritis / meningitis	*Strep suis*	penicillin	oxytetracycline
cattle & sheep	foot rot	*F. necrophorum*	penicillin	oxytetracycline

Udder

Prevention is much better than cure, as antibiotic residues are a big problem. It is rarely economically viable to treat mastitis in the most pharmacologically rational way, and a compromise between pharmacology and economics often gives the worst of both - incomplete cure and residues.

Use intramammary infusions where possible. If there are signs of systemic illness, then systemic therapy should be considered in addition to intramammary therapy. A bewildering array of preparations are available for intramammary infusion. It is usual to develop a working knowledge of the bacteria frequently causing mastitis in the herds you treat, and the antimicrobial resistances of these bacteria (by frequent cultures and sensitivity testing), although things can change from year to year.

It is necessary to decide whether to cull or to treat; or to let the infection linger sub-clinically and treat it after drying off. In many cases (about 20%) the cow is able to defeat the infection without help, although it may take longer. This is usually a matter of economics rather than pharmacology.

Before starting treatment for mastitis without systemic illness, some idea as to the causative organism is necessary. In NZ, most clinical mastitis during lactation is caused by *Strep uberis* (environmental) or *Staph aureus* (infectious). They can cause anything from a slightly raised cell count to complete destruction of the udder. *Staph* mastitis can be difficult to treat because it is often intracellular or in micro-abscesses and is difficult for the drug to reach. *Strep agalactiae* used to be very important but has been much reduced by good farming and penicillin. *Strep epidermidis* also commonly causes mastitis with much greater tissue pathology, fibrin clotting and inflammation. These cases are more difficult to resolve, require longer courses of antimicrobial therapy, and result in permanent loss of production potential.

Environmental pathogens (*Strep uberis* is commonest in NZ) usually occur just after calving. It is becoming commoner as the other pathogens are being reduced. There have been recent reports of resistance to cloxacillin developing - 17% of isolates in one survey. *Streps* often develop resistance by changing their penicillin binding proteins rather than producing ß-lactamases.

Mastitis due to *E. coli* is uncommon in NZ. American data has shown that treatment of coliform mastitis with antibiotics is not necessarily any more effective than simply stripping out all the milk from affected quarters several times per day - absorption of lipopolysaccharides from dead bacteria is what causes the problem. Treatment of cows with coliform mastitis with bactericidal antibiotics may result in increased morbidity and mortality due to antimicrobial drug induced release of endotoxins.

Staph aureus mastitis often responds to penicillins, although a significant number of isolates are resistant (about 35%) and cloxacillin (or a cephalosporin) has to be used. None of these drugs are very good at penetrating cells or abscesses to get at the bacteria: the ideal way to treat would be to give a long course of high doses or use a drug with good penetration but both treatments would result in very long withholding times. Erythromycin is a compromise which is sometimes used, pirlimycin may be better.

Sometimes the cow is dried off and the bacteria treated with dry cow intramammary preparations. These contain the same drugs but in a slow release form (usually a waxy or aluminium stearate base) and have very long withholding times (30 days). Concern has been expressed recently about dry cow therapy producing residues in bobby calves - follow the NZVA guidelines (`http://www.vets.org.nz`).

Streps are nearly always sensitive to penicillins and are easy to clear up but tend to reinfect cows.

Read the bit in the data sheet about the withholding time and tell the farmer!

animal	disease	bacteria	first choice	second choice
cows	mastitis	*Staph aureus*	cloxacillin	oxytetracycline
cows	mastitis	*Strep uberis*	penicillin	cloxacillin
cows	mastitis	*Strep agalactiae*	penicillin	erythromycin
cows	mastitis	coliforms	antibiotics do not work	
sows	mastitis / metritis / agalactia	coliforms	co-trimazine & NSAIDs	amoxycillin & NSAIDs

drug	world average	NZ heifers
penicillin	0.5	4
ampicillin	1	
cloxacillin / oxacillin	1	0.5
cephalothin	0.5	
ceftiofur	1	2
cephapirin		0.5
co-amoxyclav	<0.06	
penicillin & novobiocin	0.125	
novobiocin		1
enrofloxacin	0.125	0.25
premafloxacin	<0.0078	
erythromycin	0.5	0.5
clindamycin	1	
lincomycin	16	
pirlimycin	1	1
neomycin	2	
lincomycin & neomycin	0.5	
sulphamethazine	4	

Staph aureus *MIC_{90}s (µg/mL) for a variety of drugs. World average from Oliveiera et al., 2000,* Journal of Dairy Science, 83, *855 - 862; NZ heifers from Salmon et al, 1998,* Journal of Dairy Science, 81, *570 - 578.*

Production enhancers

Antibiotics are not just given to sick animals, there are a number of different ways that they can be used:

Treatment - antibiotics given at full doses to kill or inhibit pathogens causing disease in individual animals.

Metaphylaxis - antibiotics given at full doses to kill or inhibit pathogens in groups of healthy animals exposed to disease. Sometimes necessary.

Prophylaxis - antibiotics given at low doses to groups of healthy animals to prevent disease. Ethically dubious - often a substitute for good husbandry.

Growth promotion - antibiotics given at low doses to make animals grow faster / use food more efficiently / produce more milk solids etc. Justifiable if husbandry is good and the drugs have no chance of producing cross resistance with drugs used for treatment in man or animals, otherwise highly unethical.

Antibiotic growth promoters are sometimes called production enhancers to differentiate them from hormonal growth promoters (= anabolic steroids). They are usually narrow-spectrum (usually Gram positive) antibiotics which are added to the feed in small quantities (up to 100 grams per tonne) or administered orally, sometimes in the water. They are most widely used in pig and poultry diets and increasingly in rations for intensively reared cattle, where they stimulate growth rate, improve feed conversion efficiency and reduce feed intake. They are usually not absorbed systemically.

These agents may increase live weight gain by 3-5% in poultry, pigs and young, pre-ruminant calves (similar to gnotobiotic animals), and up to 10% in ruminating cattle. The resultant increased feed conversion efficiency reduces the time and quantity of (concentrate) feed required to rear the animal. There is no obvious benefit to grass-fed animals.

There is a continuum between drugs used to promote growth and drugs used to treat disease, despite the four groups mentioned above. Drug use to prevent disease - usually caused by poor husbandry - is tricky. If the drug use is successful, the animals stay healthy. Most drugs used for prophylaxis also have a growth promoting effect in healthy animals. Unfortunately, this type of use is widespread in NZ. There are regulatory differences in that growth promoters are regarded as safe enough for farmers to give unsupervised, but drugs for prophylaxis of disease require a vet's prescription. If you presribe these drugs, be prepared to justify yourself.

Politics

These drugs are used by the ton. In 1998 in NZ, approximately 36 tonnes of antibiotics were used for growth promotion and prophylaxis compared to a total human use of about 40 tonnes of antibiotics. This is where the veterinary drug companies make most of their money, but there is pressure from several directions to reduce their use. Consumers are becoming jumpy about eating "contaminated" meat and these drugs have been banned in Scandinavia for this reason. When these drugs first became widely used in the 1960s, it was agreed that drugs used clinically in people would not be used as production enhancers in case of resistant bacteria transferring into people. This sensible idea has lapsed a bit over the years, but as highly resistant strains of bacteria emerge in response to indiscriminate use of antibiotics by the medical profession, there is pressure for the previously obscure production enhancers to become human clinical drugs (and thus not be used as production enhancers any more). Europe has recently banned avoparcin, bacitracin, virginiamycin, tylosin and spiramycin. In NZ, except for avoparcin which is also banned here, these are mainly used in pigs and poultry, which are not exported to Europe. Growth promoters as such are being phased out in NZ.

Growth promoters are not all bad. The most complete figures are from Denmark where there is an excellent surveillance system for both animals and people. Since growth promoters were banned there in 1997, the amount of therapeutic antibiotics used in animals has almost doubled. The incidence of salmonellosis and campylobacteriosis in people has also reached a record high. Coincidence?

Mechanism of action

Most of these agents are active against Gram positive bacteria and appear to act on bacterial populations in the gastrointestinal system. Most drugs are not absorbed from the gut to any great extent so the plasma drug concentrations are low. They must be given daily in the concentrate part of the diet or administered orally (daily drenching or bolus form - cattle only). When incorporated into feed blocks or licks, individual animals may receive widely varying doses.

In monogastric species (including pre-ruminant calves) the mode of action is not clear, but the drugs are thought to act by suppressing harmful bacterial metabolites, suppressing potential pathogenic organisms, or suppressing the competition between intestinal organisms. They may also act by altering the metabolic activity of the bacterial population, or enhancing the ability of the host to absorb nutrients from the gut.

Antibacterial agents which act in the rumen rather than the lower gut are called "rumen modifiers" or "rumen-active anaboles". These compounds can be used once the rumen is fully functional (of no use in veal calves) and alter the pattern of rumen fermentation. Gram positive bacteria are major producers of the volatile fatty acids acetate and butyrate and methane gas. They decrease the microbial production of lactic acid and enhance the production of the gluconeogenic fatty acid propionate at the expense of acetate and butyrate. The reduction in the acetate-propionate ratio results in more available energy and substrate for glucose production by the liver. The reduced production of methane means less wastage

of dietary carbon and energy through eructation. These drugs are probably more relevant to cattle fed on grain than grazing animals; in fact there is no good evidence that they are likely to work in cattle under the usual NZ conditions.

Resistance

Any use of antibiotics exerts selection pressure for resistance in bacterial populations exposed to the drug. Giving antibiotics by the ton to food animals is thus a cause for concern. There is convincing evidence from Europe and the USA that antibiotic use in animals gives rise to resistance in human pathogens for a variety of Gram negative food poisoning organisms (*E coli* O157, *Salmonella* spp, *Campylobacter* spp.). The evidence for such resistance in human Gram positive pathogens such as methicillin resistant *Staph aureus* (MRSA) and vancomycin resistant enterococci (VRE) is not very convincing at the moment, although nearly all the VRE in NZ (people and chickens) seems to be the same clone. However, in sick people, the consequence of infections with these bacteria is often death. Some in the animal feed industry in the USA have expressed the view that since these are people in intensive care units who will probably die anyway, there is no need to change animal feeding practices.

Drugs

Bacitracin

Interferes with cell wall production and has a similar spectrum of activity to penicillin. Resistance has been reported in *Staphs*, *Streps* and enterococci, but problems with breakpoints make interpretation difficult. It has been in use since the 1940s without clinically significant resistance problems, although on some farms *Cl perfringens* is no longer susceptible. Its main use in NZ is the prevention of necrotic enteritis (*Cl perfringens*) in broiler chickens. It may also have some effect against *Lawsonia intracellularis* in pigs. It is not used in people, and is too toxic to give parenterally. It just been reclassified as a prescription animal remedy, and is not allowed to be used for growth promotion any more. It used to be used in milk replacers and mineral/ vitamin premixes, although there was no evidence that it was effective.

Ionophores

Particularly monensin, are used as coccidiostats (poultry and cattle), growth promoters in grain fed cattle (overseas) and to prevent bloat (cattle) and dysentry (pigs). Monensin produces a higher protein content in the milk, but reduced milk fat concentration (net result is still an increase in total milk solids) - at any rate in cattle fed rubbishy Australian diets. Resistance is not a problem. Ionophores are not used as antibacterials in people and are not prescription drugs. Remember that ionophores are toxic to horses.

The other drugs are used in much smaller quantities in NZ, but pose more of a risk if animal use leads to resistance in human pathogens.

Avilamycin

An orthosomycin which blocks protein production. Mainly active against Gram positives, although also *Borrelia* and *Legionella* spp. It is active against a wide range of multi resistant staphylococci, enterococci and streptococci. Resistance has been reported in enterococci from animals and *Strep pneumoniae* from people. No resistance has been found in *Cl perfringens*. Resistance appears to develop slowly, both *in vitro* and in the field. Used as a growth promoter in pigs and chickens. It is also useful against necrotic enteritis in chickens. It compares favourably to vancomycin *in vitro*. The equivalent human drug was withdrawn from stage 3 trials and there are no drugs of this class currently in use in people. It is not a prescription drug and can still be used as a growth promoter here.

Avoparcin

Was used as a growth promoter in chickens, pigs and cattle, and to prevent necrotic enteritis in chickens. It has also been used to improve milk production in dairy cows. It is closely related to vancomycin and teicoplanin which are used for MRSA in people. There appears to be complete cross resistance. Resistance may be transferred by VREs. The medical profession was very unhappy about the use of avoparcin in animals and it is no longer manufactured, so you should not come across it.

Dimetridazole

A nitroimidazole used to prevent swine dysentery and diarrhoea in pigs, chickens and turkeys. Resistance is rare, but there is cross resistance with metronidazole which is used in people. Dimetridazole is banned in Europe and the USA because it is carcinogenic, but is still used here. It is a prescription animal remedy.

Flavophospholipol

Also known as bambermycin, moenomycin and Flavomycin, it interferes with cell wall production, mainly in Gram positives. Its spectrum is similar to benzylpenicillin, although MRSA has been shown to be susceptible. It is used as a growth promoter in broiler chickens, turkeys, pigs and calves. Its efficacy is dubious. Resistance does not seem to develop, although there is a suggestion that it can promote cross resistance to vancomycin. Most *Clostridia* and enterococci are intrinsically resistant, although the numbers in faeces can be reduced by flavophospholipol. There are also some reports that it can reduce shedding of *E coli* resistant to other drugs. There is *in vitro* evidence that it prevents plasmid transfer. It is not used in people and is not a prescription animal remedy.

Heavy metals

Arsenic, **copper** and **zinc** have been used as growth promoters, particularly in pigs. Disposing of the faeces creates environmental problems - pig faeces on pasture can contain enough copper to kill sheep. Resistance can develop, and there is cross resistance with some antibiotics. Some *E. faecium* contain a plasmid which encodes for extra copper efflux pumps - the plasmid also contains resistance genes for tylosin and avoparcin. This means that changing from an antibiotic to copper for growth promotion can still select for antibiotic resistance.

Macrolides

Tylosin and related drugs such as **tiamulin**, are widely used in pigs and chickens as respiratory (enzootic pneumonia) and gut disease (swine dysentry) prophylactics. Other macrolides, particularly erythromycin and some of the newer drugs, are widely used in people. There is extensive, but not complete, cross resistance. All of these drugs require a prescription, you must make sure that you have a sound reason to give them before writing a prescription.

Other drugs

Oxytetracycline is often misused to prevent diarrhoea in calves and piglets, and respiratory diseases in poultry. It also has a growth promoting effect. It requires a veterinary prescription. Long courses of the drug require long withholding times.

Quinoxalines, such as **carbadox** and olaquindox, and related compounds such as **dinitro-o-toluamide** and **nicarbazin**, are used for diarrhoea (swine dysentry) and coccidiosis prophylaxis in pigs and chickens. They are mainly effective against G -. They are probably carcinogenic and are not used in people. They are not used much and there is little modern information about them. No prescription required.

Virginiamycin

A streptogramin closely related to the human drug dalfopristin / quinupristin (Synercid). It only kills Gram positives, including *Staphs*, *Streps* and enterococci, although some *E faecium* are intrinsically resistant. Resistance in enterococci develops quickly and has also been reported in *Staphs*. Virginiamycin was used as a growth promoter in pigs, chickens and turkeys, and is still used to prevent laminitis in horses. It can also prevent necrotic enteritis in chickens. Resistance to virginiamycin confers full resistance to dalfopristin / quinupristin, which has become the drug of last resort against MRSA and VRE in people. Virginiamycin is a prescription animal remedy which can only be used in horses, or for metaphylaxis of necrotic enteritis in chickens after culture and sensitivity indicates that nothing else would work, and MAF have been informed.

Clinical use

Unless the law changes, it is unlikely that vets will be involved in the use of growth promoters as such (but the WHO recommends that all antibiotics given to animals should be under veterinary control). NZFSA's current policy in NZ is to phase out most growth promoters and to only license the (same) drugs for prophylactic use under veterinary prescription.

If you are involved in advising on growth promoters, or if you prescribe antibiotics to prevent disease, it is sensible to follow the guidelines below (based on BVA guidelines since the NZVA have not got their act together yet):

Growth promoters

(1) Antibiotic growth promoters should only be used where husbandry and feeding are optimal - they should not be used to compensate for the growth retarding effects of disease, poor nutrition or poor housing.

(2) The inclusion rates and feeding instructions must be followed.

(3) There should be periodic review of the benefits of growth promoters as prices (feed, antibiotics & products) alter, as husbandry systems (housing, disease, management, nutrition etc) improve and as new knowledge becomes available.

Prophylactics

(1) Antimicrobial usage should always be part of, and not a replacement for, an integrated disease control programme. Such a programme is likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination, etc.

(2) Continued antimicrobial use in such control programmes should be regularly assessed as to effectiveness and whether their use can be reduced or stopped.

(3) Protocols should be agreed between the veterinary surgeon and the client as to when veterinary involvement is required in on-going disease conditions. These protocols must be regularly and frequently reviewed and updated.

(4) Protocols should be agreed and documented for treatment of all endemic conditions on the farm or other livestock-rearing or production premises. These protocols must be regularly reviewed and updated.

(5) Use of antimicrobials for the prevention of disease can only be justified where it can be shown that a particular disease is present on the premises, or is likely to become so, and that strategic antimicrobial use will prevent clinical outbreaks of that disease.

(6) Antimicrobials need to be used with care to maintain their efficacy. If possible, look for alternative methods of disease control (eg, vaccination) to reduce antimicrobial use.

(7) Should there be recurrence of disease following successful control of an outbreak, it will need to be investigated thoroughly to ascertain why this has occurred and the most suitable therapy to be used.

Check if there are withholding times and tell the farmer!

A pill in a jam sandwich is better than tons of antibiotic in the feed!

Antifungal drugs

Probably the most commonly encountered fungal disease is ringworm, which is usually treated with griseofulvin systemically, although a variety of topical agents are sometimes used. Other topical infections include candidiasis and some cases of otitis externa, natamycin or nystatin are usually used for these. Clotrimazole is sometimes used for other superficial infections. Systemic fungal infections are rare but potentially life threatening, the imidazoles are usually used, although amphotericin is sometimes still used because it is cheaper. The imidazoles have superseded the other drugs in human medicine but are relatively expensive since long courses of treatment are often needed for fungal infections. In human medicine, resistance is starting to emerge as a problem - this has not happened in veterinary medicine yet.

A variety of other substances can inhibit fungi to some extent, these are often seen as poisoning cases after home cures for ringworm have gone wrong!

Griseofulvin

Griseofulvin is microtubular toxin which inhibits mitosis. Inhibits growth rather than killing fungi, so has to be given for a long time. (nb duration of treatment needs to be longer with some species of dermatophytes eg, *Microsporum*, than others, eg, *Trichophyton*). It is deposited in keratin precursor cells and concentrated in the stratum corneum of skin, hair and nails, thus preventing fungal invasion.

Spectrum of activity

Fungal infections, particularly ringworm. It is probably toxic to many other cell types, including mammalian.

Toxicity

Teratogenic, therefore contraindicated in pregnant animals. **Warn female owners about handling the drug**. Diarrhoea, depression and anorexia have been reported. Sometimes damages liver.

Pharmacokinetics

Griseofulvin is variably absorbed after oral administration. Absorption is markedly enhanced by fat in the gut, so it is recommended to give griseofulvin with a fatty meal. Most absorbed drug is inactivated in the liver (first pass effect) and an inactive metabolite is excreted in the urine. Induction of mixed function oxidase enzymes increase this inactivation.

Pharmaceutical considerations

Griseofulvin itself induces hepatic mixed function oxidase enzymes, resulting in altered kinetics of other drugs.

Indications

Ringworm

Polyenes

Amphotericin B, **natamycin** and **nystatin** are polyene antibiotics active against fungal pathogens. They bind to ergosterol, the main sterol of fungal cell membranes (analogous to cholesterol of mammalian cells) and thereby disrupt the spatial configuration of the phospholipids, creating an hydrophilic channel through the membrane. The consequent leaking of potassium results in cell death.

Spectrum of activity

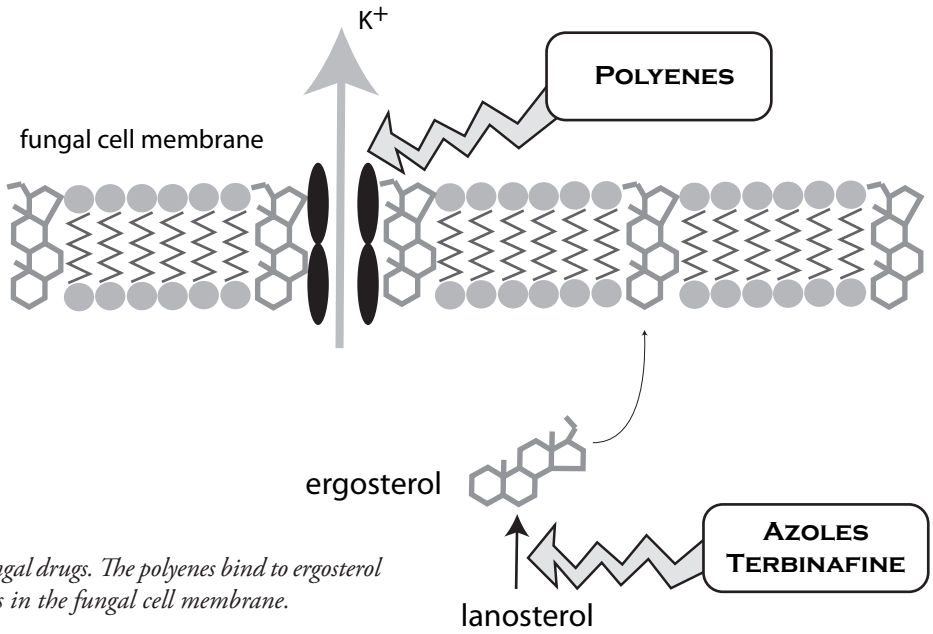
Amphotericin B is usually active against: *Candida* spp., *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Aspergillus* spp., *Mucor* spp., and *Rhizopus* spp. It may also have some antiviral effect.

Nystatin is usually active against: *Candida* spp., *Histoplasma*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces*, *Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp.

Natamycin is mainly used for *Malassezia* and *Candida* infections. It is also active against *Trichomonas*.

Toxicity

Amphotericin is a highly nephrotoxic drug, causing distal renal tubular damage resulting in loss of urine concentrating ability, hypokalaemia and hypomagnesaemia. Red and white



Sites of action of antifungal drugs. The polyenes bind to ergosterol and create ion channels in the fungal cell membrane.

blood cells, albumin and tubular casts appear in the urine. Plasma creatinine and K^+ levels should be monitored daily. Clinical signs of poor tolerance include vomiting, diarrhoea and depression. Therapy for toxicosis includes withdrawal of treatment. Flucytosine is sometimes given with it as they are synergistic and the amphoteracin dose can be reduced.

Pharmacokinetics

Amphotericin B is highly lipophilic, and therefore has a large volume of distribution (it is not distributed to the cerebrospinal fluid - intrathecal injections are necessary to achieve therapeutic concentrations). It is slowly released from lipid membranes, and therefore has a protracted mean residence time. The elimination phase half life for this drug can exceed 15 days.

Nystatin is too toxic for parenteral use. Almost none is absorbed after topical or enteral administration. The oral route is used for treating intestinal candidiasis, which can occur after cancer chemotherapy.

Pharmaceutical considerations

Amphotericin B must be reconstituted with 5% dextrose, or water. Once reconstituted it is only stable while refrigerated for up to 7 days. The daily dose is administered in 5% dextrose by intravenous infusion over 4 to 6 hours. Usually the drug is given every second day until a total dose is achieved.

Indications

Amphotericin - systemic fungal infections. A nasty drug - avoid if possible

Nystatin - topical and gut (*Candida*) infections

Natamycin - fungal otitis (*Malassezia*)

Azoles

Miconazole, clotrimazole, ketoconazole, fluconazole and **itraconazole** are synthetic imidazoles or triazoles, whose structure is similar to the benzimidazole anthelmintics. (Thiabendazole is used as an antifungal in the food industry.)

Mechanism of action

The azoles inhibit the specific cytochrome P450 enzyme of the fungi which demethylates lanosterol, the precursor of ergosterol, thereby inhibiting ergosterol synthesis. Ergosterol is necessary for normal cell membrane integrity. In mammalian cells this inhibition results in suppressed cholesterol synthesis, but mammals are able to utilise dietary cholesterol, whereas fungi are obliged to synthesise their own ergosterol. Furthermore, compared to fungal sensitivity 600 x concentrations are needed to inhibit mammalian cholesterol synthesis.

Spectrum of activity

Azoles have a broad antifungal spectrum of activity. They are usually active against: *Candida* spp., *Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp. *Pityrosporum* spp. Azoles are either fungistatic or fungicidal, depending on dose.

Imidazoles (but not triazoles) also kill *Nocardia* and *Rhodococcus*.

Toxicity

Miconazole and clotrimazole are only used topically, where they occasionally cause local irritation.

Ketoconazole can cause anorexia, vomiting and depression. Cats are more sensitive than other species. Avoid in liver disease - hepatic enzymes may be mildly elevated. Ketoconazole inhibits cytochrome P450 enzymes, and may lead to accumulation of other co-administered drugs, through inhibition of their hepatic clearance. It is sometimes used deliberately to inhibit the metabolism of expensive drugs such as cyclosporin.

Pharmacokinetics

Almost none is absorbed after topical administration. Topical administration for fungal infections of nails is unlikely to be beneficial because of poor penetration into this tissue.

Ketoconazole is absorbed well after oral administration, however this absorption is dependent on an acid environment. Histamine H2 blockers, such as cimetidine, will impede the absorption of ketoconazole. It is highly protein bound (80%) and is poorly distributed to the central nervous system.

Pharmaceutical considerations

Miconazole, fluconazole and clotrimazole are available in a variety of topical preparations. Ketoconazole is available as tablets for oral use.

Indications

Systemic mycoses (ketoconazole, itraconazole), ringworm (miconazole, fluconazole), nasal aspergillosis (clotrimazole, itraconazole), severe yeast otitis (clotrimazole).

Other antifungals

Terbinafine is sometimes used in people to treat dermatophyte infections. It also inhibits fungal sterol production and may be synergistic with the azoles. It is only fungistatic against yeasts. Limited info on its use in animals.

Flucytosine is sometimes used for systemic yeast infections. Resistance develops quickly, so it is always given with amphotericin - the two are synergistic.

Lufenuron is a chitin inhibitor sold for killing fleas. Fungi also use chitin, and it has been tried in difficult fungal infections in cats with some success.

Caspofungin is a new human drug which claims to combine the efficacy of amphotericin and the safety of the azoles. No experience in animals yet.

Sodium **iodide** is sometimes used for actinobacillosis and actinomycosis. Its mechanism of action is unknown.

Antiviral drugs

There are not many of these (at the moment) which are clinically useful in veterinary medicine. Many drugs work *in vitro* but are too toxic to use *in vivo*. Most drugs used in people are virostatic.

Drugs which stop transcription

Idoxyuridine is active against DNA viruses and is used in people for coldsores (herpes). Systemic use causes leukopaenia, liver damage and gut upsets.

Cytarabine is a nucleoside analogue which inhibits DNA polymerase. It is effective against herpes, pox viruses, vaccinia, rabies, cytomegaloviruses and probably hepatitis B virus *in vitro*, but is only used for herpes keratitis or encephalitis (and as an anti-cancer drug). **Vidarabine** is available as an opthalmic ointment for herpes.

Acyclovir is effective against herpes viruses and is sometimes used to treat ocular herpes in cats (Zovirax eye ointment). It, and the related **gancyclovir**, are also used for cytomegaolovirus infection in people.

Zidovudine (AZT) is a reverse transcriptase inhibitor which has been used to treat feline AIDS and FeLV. In combination with interferon α 2b, it appears to improve the cats' condition. It is toxic to the bone marrow - adverse effects include anaemia and granulocytopaenia. It should not be given for more than 3 weeks and blood counts checked regularly. **Lamivudine** is used for hepatitis B in people in NZ. Resistance has already been reported to zidovudine and lamivudine - 27% of AIDS cases in people in the UK. **Nevirapine** is another reverse transcriptase inhibitor available here - no experience in animals.

Interferon

Interferons are glycopeptide molecules produced by animals in response to certain infections. They must be given parenterally as they are mostly inactivated in the stomach. They are used for a variety of viral infections in people: they have also been used in cats with FeLV, usually in combination with zidovudine.

Other drugs

Zanamivir is a neuraminidase inhibitor which inhibits the release of influenza viruses from respiratory epithelium. It is given to people as a powder for inhalation so veterinary application would be difficult. There are sveral similar drugs on their way.

Nelfinavir is an HIV protease inhibitor used in AIDS patients - no animal experience.

Amantadine is used in people for flu viruses, although resistance has already been demonstrated. This has not been helped by illegal feeding to chickens in China to prevent bird flu. Amantadine is also an effective NMDA antagonist and has bencome trendy in the USA as part of a balanced analgesic technique. Use amitrptylline instead for this and keep the amantadine for viruses.

Cases to think about

Standardbred foal

Description: one week old male

History: foal was normal until yesterday, other than leaking urine from umbilicus for two days after birth. Yesterday developed swelling of the left hock, and is now very lame in that leg.

Clinical Exam: The foal is lame with a fluid swelling of the tibiotarsal joint, febrile with a moist exudative umbilicus.

Q1: List the problems you can identify.

Your initial diagnosis is septic arthritis of the left tibiotarsal joint, probably secondary to umbilical infection (in this case) and bacteraemia. No other joints appear to be infected.

Q2: What bacterial samples could you take?

Q3: How would you take these, and get them to the lab?

X rays of the left hock show no lesions ofosteomyelitis. An ultrasound scan of the umbilicus shows fluid accumulation around the umbilical remnant, suggestive of umbilical abscess.

Q4: What immediate treatment would you give while waiting for results of culture and sensitivity? What problems might be anticipated with the antibiotics you choose? What precautions might you take?

Culture: Joint fluid - *E coli* (1), blood - *E coli* (2) *Bacillus* spp. (3), umbilical fluid - *E coli* (4)

Antibiotic MICs µg/mL	***1,2,4***	***3***
ampicillin	2	1
penicillin	>64	0.5
amoxycillin	2	1
co-trimazine	1	0.4
gentamicin	0.25	0.1
amikacin	0.25	0.1
erythromycin	>64	0.032
cephalothin	4	1
oxytetracycline	4	2
enrofloxacin	0.016	0.4

Q5: What antibiotic treatment would you choose for the foal? Your choice should be based on practical considerations as well as sensitivity patterns. Estimate the duration of therapy.

Scottish Terrier Snapper

Description: 10 years old entire male

History: Been treated empirically by the referring vet "on and off" for 8 months for urinary cystitis, diagnosed by history of dysuria and presence of protein in the urine. Amoxycillin, co-trimazine and enrofloxacin have each been used separately for six or seven day courses; each caused a clinical improvement followed by an interval before recurrence.

Q1: List the problems you can identify.

Clinical Exam: Bilaterally symmetrical but large prostate, bladder wall slightly thickened and dysuria. Otherwise normal.

Q2: Now list the problems you can identify.

Culture: Urine culture - *E. coli* (1), *Proteus* spp (2)

Antibiotic MICs µg/mL	***1***	***2***
amoxycillin	16	>32
carbenicillin	>32	>32
cephalothin	16	1
cefadroxil	0.5	0.5
erythromycin	1	16
gentamicin	2	>32
amikacin	1	2
co-trimoxazole	0.5	0.5
tetracycline	2	4
nitrofurantoin	>32	8
norfloxacin	0.08	0.08

Q3: What other clinical pathology test would be most likely to be beneficial to your diagnosis?

Q4: Which of the resistances reported would you have expected, and why? Are any of the reports surprising?

Q5: Choose an antibiotic or combination of antibiotics to treat Snapper and design dosage regime for him. Justify your decisions.

Q6: What are the limitations of in vitro antibiotic sensitivity testing?

NZ white rabbit

Description: pet doe about 1 yr old

History: The rabbit has been sneezing off and on for three weeks (it is summer, the weather has been hot for several weeks and more recently humid). The owner has noticed a discharge from the nose for the last day or two. The rabbit has a decreased appetite and activity.

Clinical Exam: The rabbit has a mild conjunctivitis, mucopurulent nasal discharge, appears depressed and the fur on the medial aspect of the front paws is wet and matted. There is an increase in temperature (40.5˚C).

Q1: List the problems you can identify.

Q2: What samples would you take to determine the cause of infection?

Q3: How would you take the sample(s)?

Q4: What treatment would you begin while waiting for culture results? Route of administration? What problems, if any, would you anticipate from your choice(s)? Are there any contraindications to antibiotics in the rabbit?

Culture: *Pasteurella multocida*

Antibiotic sensitivity	
benzylpenicillin	s
amoxicillin	s
gentamicin	s
erythromycin	s
tetracycline	r
enrofloxacin	s

Q5: what antibiotic therapy would you consider for this patient? This is a pet rabbit (only one in the household) and the client is somewhat concerned about cost, but is willing to do what is best for the family and the pet. What advice should you give the client concerning drug treatment, follow up care and zoonoses?

Great Dane Fergus

Description: 7 yr, female spayed

History: The dog had been normal up until a spay 4 weeks previously. 1 week after the operation, the dog developed a fever (39.9˚C), a poor appetite and reluctance to move. A 7 day course of enrofloxacin was prescribed by the referring vet but little improvement was noticed. On physical examination, the dog had injected brick red mucous membranes, was tachycardic (156 bpm), febrile (40.2˚C) and had a weak pulse. Capillary refill time was very rapid (<0.5secs). She was hyperaesthetic, unwilling to move, and had a swollen right elbow. Haematology showed a mild leucocytosis. Blood biochemistry was normal.

Q1: List the problems you can identify.

Interim Summary: In view of the major problems identified the clinician in charge suspected Fergus was septic. This decision was based on the elevated body temperature and evidence of hyperdynamic shock (brick red mucous membranes, tachycardia, brisk

capillary refill time, and weak pulse). Many other conditions (eg immune-mediated disease, neoplasia, stress) can result in elevated body temperature but these are usually not associated with hyperdynamic shock. The swollen elbow was considered most likely to be due to infectious arthritis although trauma, neoplasia, or immune-mediated arthritis could not be ruled out. The plan adopted was to acquire diagnostic samples for culture and then to embark on a search for a source of the infection (via cardiac ultrasound, abdominal radiographs & ultrasound, spinal radiographs etc).

Q2: Comment on the referring veterinarian's choice of enrofloxacin for the

initial treatment of this dog.

Q3: What 3 tissues or fluid samples would you take to determine the responsible agent?

Q4: Having obtained your diagnostic samples what antibiotic(s) would you empirically choose (ie prior to the sensitivity pattern) to treat this dog's suspected septic shock and by what route would you give them?

Q5: A Staph aureus *was cultured from 2 of these diagnostic samples. 5 days later, the sensitivity pattern listed below became available. By this time Fergus was starting to improve. No focus of infection was found but the suspicion remained that there may be a misplaced swab in the abdomen or an early discospondylitis lesion. What antibiotic would you use now and for how long?*

Antibiotic sensitivity

ampicillin	r
co-trimazine	s
chloramphenicol	s
gentamicin	s
enrofloxacin	s
cephalexin	s
co-amoxiclav	s

Thoroughbred colt

Description: valuable yearling

History: The colt has had a nasal discharge and cough for 2 days and won't eat. "Oh, and while you're here, two of our other yearlings have just gone off their feed as well." (There are 12 in the paddock)

Clinical Exam: The 3 affected yearlings have elevated rectal temperatures, cough, laboured respiration, and purulent nasal discharge. Two also have tense swelling of the lymph nodes around the mandible and throat region. In one of these yearlings, one lymph node is draining thick purulent material. The nine other yearlings, from a distance, seem to be unaffected.

Q1: What problems can you identify?

Q2: What further physical examination procedures will you do now (if any)?

Q3: What clinical pathology and bacteriology tests will you perform?

Three yearlings appear to require immediate treatments

Q4: What treatment will you give while waiting for results of tests?

Q5: How will you manage unaffected yearlings?

Culture: *Streptococcus equii*

Antibiotic sensitivity:

penicillin	s
ampicillin	s
tetracycline	s
co-trimazine	s
gentamicin	r
erythromycin	s

Q6: Choose the most appropriate treatment, including dosage and route of administration. Justify your choice.

Q7: What problems might you anticipate with the treatment you chose?

Q8: What problems are associated with administration of oral antibiotics in horses (other than foals)?

DSH cat Minnie

Description: 3 yr, female spayed

History: Minnie was presented with the primary complaint of diarrhoea. She had been vaccinated against panleucopaenia on an annual basis. The diarrhoea was acute in onset, was voluminous and contained fresh blood and mucus. Frequent straining to defaecate had been observed. On physical examination the cat was determined to be depressed, dehydrated and febrile (40.2°C). Liquid faeces and excessive gas could be palpated throughout the intestinal tract. Haematology showed a leucopaenia but no other abnormalities.

Q1: List the problems you can identify.

Q2: Do these clinical signs point to small bowel-type diarrhoea, large bowel-type diarrhoea or both (enterocolitis)?

Q3: What are 3 potential infectious causes of these signs?

Q4: Would you place the cat on antibiotics prior to the culture results? If so, which antibiotic and by what route?

Q5: Do antibiotics have any adverse consequences on the GI tract? If so, list 2 adverse effects.

Q6: What is a pharmacokinetic property of certain antibiotics that increases the likelihood of adverse effects on the normal flora?

Q7: What antibacterial spectrum of an antibiotic (io aerobic, anaerobic, gram +ve, gram -ve) will Increase the likelihood of adverse effects on the normal flora?

Q8: How would you confirm a bacterial enterocolitis?

Interim summary: Because of the clinical signs, an infectious enteritis was suspected and a faecal culture for enteric pathogens was submitted. A *Salmonella* species was cultured after 3 days incubation. No sensitivity pattern was available.

Q9: Would you continue antibiotic treatment once the diagnosis of salmonellosis has been made?

Q10: What antibiotic would you use to treat Salmonella *in this cat if you decided to treat*?

King Charles Cavalier Spaniel Charlie

Description: 10 years old, overweight, entire female

History: Charlie has a poor appetite but is bright. She has recently been on heat and there was a misalliance. She is polyuric and polydipsic and there is a discharge from her vulva.

Q1: List the problems you can identify

Clinical Exam: Charlie is panting though it is not a hot day and she is not nervous. Her abdomen is distended and hard to palpate. There is a purulent discharge from her vulva. Temperature 38.9°C; Heart Rate 160. Your provisional diagnosis is a pyometra.

Q2: Now list the problems you can identify. What clinical pathology tests could you use? What will you treat Charlie with while you wait for the results? Why?

	Haematology:	Normal Range
Hb	9.5 g/dl	12-18
PCV	0.25	0.37-0.55
RBC	$4.22x10^{12}$/l	5.5-8.5
MCHC	38.0 g/dl	32-36
Total Protein	90 g/l	60-75
Fibrinogen	9 g/l	1-4
PP:F	9:1	
Reticulocytes	2.1 x 10^9/l	
WBC	55.3 x 10^9/l	6-17
Neutrophils		
- segmented	48.6(88%)	3-11(70%)
- bands	2.76(5%)	0-0.3(0.07%)
Eosinophils	0.55(1%)	0.1-1.25(2-10%)
Lymphocytes	1.66(3%)	1-4.8(12-30%)
Monocytes	1.66 (3%)	0.5-1.35(3-10%)

Q3: What do these total and differential white blood cell counts

indicate? Are there any other problems here? What other routine diagnostic tests could you use to confirm your diagnosis?

Q4: What are your treatment options? What is the likelihood of success with conservative treatment?

Q5: Choose an antibiotic or combination of antibiotics with which to treat Charlie and design a dosage regime for her for each treatment option. Justify your decisions.

Friesian cow No. 267

Description: four years old, high yielder

History: Cow had a difficult calving 2 weeks ago and was down with calving paralysis for 10 days. She is now able to walk around but she is still being milked by hand in the paddock. This morning the farmer noticed that she has a hot, swollen quarter and was difficult to milk. The farmer suspects mastitis but hasn't treated her yet because he has run out of intramammary antibiotics. This cow has never had mastitis before.

Clinical Exam: Cow is in poor condition but appears bright and alert. Temperature is 39.1˚C, heart rate and respiratory rate are normal. the left-hand back quarter of the udder is hot, swollen and painful and the milk from this quarter is watery and,contains white flecks.

Q1: Given that you agree with the farmer's diagnosis of mastitis what would you do next?

Being an astute clinician you realise that acute mastitis is most commonly caused by either *Streps*, *Staphs* or rarely *E.coli*.

Q2: What immediate treatment would you give? Give doses, route of administration and duration of therapy. You have the following antibiotic preparations available:

Intramammary:	Parenteral:
cloxacillin & neomycin	procaine penicillin
penicillin, streptomycin	co-trimazine
ampicillin, cloxacillin	streptomycin/penicillin
co-amoxiclav, prednisolone	erythromycin
cloxacillin	oxytetracycline

Do you think it is necessary to administer parenteral antibiotics? Why?

Q3: What factors determine a drug's distribution from blood into milk?

Culture: *E.coli*

Antibiotic sensitivity	
penicillin	r
ampicillin	s
cloxacillin	r
amoxicillin	s
streptomycin	r
neomycin	r
co-trimoxazole	s
erythromycin	r

Q4: Would you now change your initial treatment plan based on these results? If so, what would be your new treatment plan?

Q5: Apart from spectrum of activity what other important factor do you need to consider and make the farmer aware of when selecting and administering antibiotics to dairy cows?

German Shepherd dog Kaiser

Description: 6 year entire male

History: Kaiser had an acute onset of pain in his abdomen and hind legs 2 weeks ago and has been referred to you by another vet. The history is that he was presented to one vet in a practice and had a temperature of 40˚C and was treated with a non-steroidal anti-inflammatory (flunixin) and antibiotics (amoxicillin). He returned to the same clinic and saw another vet 3 days later with no improvement, was hunched when walking and resented hind limb and abdominal palpation and manipulation of the neck. A blood sample was taken and radiographs of the cervical spine and hips showed no clinical changes. Because Kaiser appeared bright and alert and was moving freely there was no further treatment and he was sent home. The blood results showed an acute inflammatory change with a slight neutrophilia and as the owners felt the dog was starting to stiffen up co-trimoxazole and a steroid(prednisolone) was dispensed 5 days after the second visit. Three days later there appeared to be no improvement, Kaiser had fallen down some steps and was in pain again.

Q1:List the problems of Kaiser that you can identify.What do you think of the referring vets pharmacological therapy. Why?

Clinical Exam: From your examination Kaiser is reluctant to stand, is hunched in the back while standing and resents any caudal hindlimb extension or pressure on his lumbar spine. There does not appear to be any abdominal pain. He takes short strides when walking and has normal neurological findings.Temperature is normal. One of your differential diagnosis is discospondylitis.

Q2: Now list the problems you can identify. What clinical pathology tests could you use? What other diagnostic aid will you use? What will you treat Kaiser with while you wait for the results? Why?

Q3: What would you expect to see in your other diagnostic aid? Why may it differ from when the dog first presented?

Q4: Choose an antibiotic or combination with which to treat Kaiser and design a dosage regime for him. Justify your decisions.

Labrador retriever Dribbles

Description: 8 yr, female,

History: You are presented with Dribbles, with a history of chronic skin infections. She has been treated by your employer over the past several months empirically, using erythromycin or chloramphenicol for an isolated penicillinase.producing *Staphylococcus intermedius*. The dog also has had an intractable outer ear infection, which has been treated with gentamicin ear drops twice daily for two months. Dribbles owners tell you that she seems to be depressed, and has not "moved around much lately".

Q1 List the problems you can identify with this dog.

Q2 Defend or criticise your boss's approach to therapy.

Clinical exam: Dribbles is overweight. She is cold to touch and has a sparse, patchy hair coat. She has large patches of exudative purulent dermatitis on her flanks and ventral abdomen. Her external ear canals are full of a green smelly purulent material: she resists them being examined. Her heart rate is 54 bpm at rest. You suspect that Dribbles may be hypothyroid. You know that hypothyroidism can cause decreased cell mediated immunity, and you suspect this might be occurring in Dribbles.

Q3 List the additional problems you can identify now.

Q4 Should you do anything diagnostically or therapeutically about the hormonal disorder at this time and why?

Q5 Should you do anything differently about the skin and ear infections at this time? If so, what and why?

Q6 Indicate your course of therapy if the owner has no money and cannot afford diagnostic tests at all, i.e. what is your recommended empirical therapy?

Culture: skin (1) *Staphylococcus* and ear (2) *Pseudomonas*.

Antibiotic sensitivity	*1*	*2*
Amoxicillin	r	r
Oxacillin	s	r
Carbenicillin	r	r
Cephalothin	r	r
Cefoxitin	s	r
Erythromycin	r	r
Gentamicin	s	r
Amikacin	s	s
Co-trimoxazole	s	r
Tetracycline	s	r
Nitrofurantoin	s	s
Norfloxacin	s	s

Q7 Define your recommended therapeutic regime now.

Practice exam questions

Multiple choice questions

1. Benzylpenicillin
   - is effective when given orally ❑
   - is metabolised rapidly in the neonate ❑
   - is usually injected iv ❑
   - excretion may be reduced by probenecid ❑
   - crosses the blood brain barrier easily ❑

2. Contra-indications for tetracyclines include
   - neonatal animals ❑
   - pregnancy ❑
   - pigs ❑
   - anaemia ❑
   - *Mycoplasma* infection ❑

3. Enrofloxacin
   - inhibits integrase 1 ❑
   - is a prodrug for carbapenem ❑
   - is bacteriostatic at low doses but bactericidal at high doses ❑
   - is effective against *E. coli* ❑
   - is ineffective against *Bacillus* spp. ❑

4. Chloramphenicol
   - must be administered parenterally ❑
   - can be safely used in neonates ❑
   - does not penetrate the blood brain barrier ❑
   - can cause depression of bone marrow function ❑
   - can cause discolouration of developing teeth in pups ❑

5. Sulphonamides
   - inhibit the incorporation of PABA into the bacterial 30S ribosomal subunit ❑
   - antagonise the action of tolbutamide ❑
   - are excreted more rapidly in acid urine ❑
   - are secreted into milk ❑
   - are bactericidal ❑

6. Streptomycin
   - may cause blindness ❑
   - may potentiate neuromuscular blockade ❑
   - is used to treat strangles ❑
   - is cardiotoxic ❑
   - should not be given to cats ❑

7. Penicillins are generally useful against
   - *Streptococcus equii* ❑
   - *Escherichia coli* ❑
   - *Pseudomonas aeruginosa* ❑
   - *Mycobacterium tuberculosis* ❑
   - *Brachyspira hyodysenteriae* ❑

8. Chlortetracycline
- inhibits both Gram positive and negative bacteria ❑
- may be given to gerbils in their drinking water ❑
- is bactericidal ❑
- should be given with milk in young animals ❑
- has a zero withholding time in pigs ❑

9. Framycetin is
- a semi-synthetic penicillin ❑
- usually given intravenously ❑
- likely to be effective in treating diarrhoea in calves ❑
- active against *Staphylococcus aureus* ❑
- also effective against a wide variety of protozoa ❑

10. The following may be mixed in the feed of laying hens as growth promoters
- penicillin ❑
- flavophospholipol ❑
- virginiamycin ❑
- carbadox ❑
- none of these ❑