BVSC & AH STUDY BOOK 3 OF 7

Chemotherapy: Antimicrobial, Antiparasitic and Anticancer Drugs

Nineteen chapters on the drugs that kill or control microbes, parasites and cancer cells, together with resistance, residues and food safety. Each chapter explains the mechanism, the clinical meaning and the species cautions, and ends with a 10-question self-test.

19 chapters | **190** practice questions | **No** dose tables

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Start here

Pick a chapter from the list on the left (or the top bar on a phone). Chapters 1 and 9 are the thinking chapters: how to choose an antibiotic and how to protect it. Chapters 2 to 8 cover the antibacterial classes, chapters 10 and 11 cover residues and mastitis, chapters 12 to 16 cover antifungal, antiviral and antiparasitic drugs, and chapters 17 to 19 cover disinfectants, cancer drugs and immune drugs. Each chapter has six parts: Learn, Concepts, Compare, Species, Quiz and Revise. Your quiz progress is saved on this device only.

CHAPTER 1 OF 19

Principles of chemotherapy and antibiotic selection

The reasoning behind choosing an antibacterial drug: spectrum, killing versus inhibiting, the PK/PD indices that predict success, laboratory sensitivity testing, biofilms, combinations and the rules for prophylaxis. It builds the stewardship mindset used in every later chemotherapy chapter.

After this chapter you can

- Define spectrum and explain why narrow spectrum is preferred when the pathogen is known
- Distinguish bactericidal from bacteriostatic action and state when the difference matters
- Explain concentration-dependent and time-dependent killing as PK/PD concepts
- Interpret MIC and disc diffusion results and their limits
- Describe how biofilms, combinations and prophylaxis affect antibiotic choice

Selective toxicity and the logic of choice

Chemotherapy means using chemicals that harm an invader more than the host. This property is called **selective toxicity**. Antibacterials achieve it by attacking structures or pathways that bacteria have and animal cells lack or have in a different form, such as the cell wall, the bacterial ribosome or folate synthesis.

Choosing an antibiotic is therefore a chain of questions. Is there really a bacterial infection? Which organism is likely? Will the drug reach the infected site at a useful concentration? Is the drug safe in this species and this production class? Finally, is the choice defensible in terms of resistance and residues?

A common student error is to start from the drug name. Start from the patient and the site of infection, then work towards the drug.

Spectrum of activity

The **spectrum** is the range of bacteria a drug can act against. A *narrow-spectrum* drug acts on a limited group, for example mainly Gram-positive organisms. A *broad-spectrum* drug acts on many groups, including Gram-positive, Gram-negative and sometimes anaerobes or atypical organisms.

Broad spectrum sounds attractive but has costs. It disturbs the normal flora, particularly in the gut, which can cause diarrhoea, overgrowth of resistant organisms and loss of colonisation resistance. It also exerts selection pressure on many bacterial species at once, so it favours resistance more widely.

The principle is to use the **narrowest spectrum that covers the likely or proven pathogen**. Spectrum is not fixed forever: acquired resistance can remove a species

from a drug's useful spectrum, so a textbook spectrum is only a starting guide.

Gram-negative bacteria have an outer membrane that many large or hydrophilic molecules cannot cross, which is one reason some Gram-positive-active drugs fail against them.

Bactericidal and bacteriostatic action

A **bactericidal** drug kills bacteria. A **bacteriostatic** drug stops multiplication and relies on host defences to clear the organisms. Examples usually placed in the first group are beta-lactams and aminoglycosides; in the second, tetracyclines and macrolides at ordinary concentrations. Many drugs sit between the two depending on concentration and organism.

The distinction is laboratory-defined, based on the relation between the MIC and the minimum bactericidal concentration. It is a spectrum, not a strict label.

Clinically the difference matters most when host defences are weak: neutropenia, endocarditis, meningitis, severe sepsis or infection in poorly perfused tissue. In such cases a bactericidal drug is preferred. In a healthy animal with a localised infection, a bacteriostatic drug usually works well.

Common confusion: never combine a drug that needs actively dividing bacteria to kill (such as a beta-lactam) with one that halts growth without good reason, since the second may blunt the first. This is a theoretical antagonism that has real support in some infections but is not universal.

Pharmacokinetic and pharmacodynamic principles

Pharmacokinetics describes what the body does to the drug, and **pharmacodynamics** what the drug does to the bacteria. **PK/PD** links the two so that we can predict success.

Antibacterials follow two broad killing patterns:

- **Concentration-dependent killing.** Higher peak concentration relative to MIC gives faster, greater killing. Aminoglycosides and fluoroquinolones are classic examples. The useful indices are peak to MIC and area under the curve to MIC. These drugs often have a post-antibiotic effect, meaning bacterial growth stays suppressed after levels fall.

- **Time-dependent killing.** Killing depends on how long the concentration stays above the MIC, because the effect saturates at a few multiples of MIC. Beta-lactams are the standard example. The useful index is the time above MIC.

This is why dosing schedules differ between classes. We do not need numbers here; the idea is that peak matters for the first group and duration matters for the second.

The drug must also reach the **site of infection**. Fluoroquinolones and macrolides penetrate cells and tissues, while beta-lactams and aminoglycosides stay mostly in extracellular fluid. Pus, necrotic tissue and low oxygen reduce the activity of some drugs, notably aminoglycosides.

Culture, sensitivity, MIC and biofilms

Whenever practical, take a sample *before* starting treatment and send it for **culture and sensitivity**. Poor sampling and prior antibiotic use are the commonest reasons for misleading results.

The **minimum inhibitory concentration (MIC)** is the lowest drug concentration that prevents visible growth in a standard test. A lower MIC means the organism is more susceptible, but MICs of different drugs cannot be compared directly. A result is read against *breakpoints* set by a standards body, giving the categories susceptible, intermediate or resistant. The breakpoint takes into account the drug's achievable concentration, so it is drug-, species- and often site-specific.

In **disc diffusion** (Kirby-Bauer), a disc of drug is placed on an inoculated agar plate. The drug diffuses outward and the diameter of the clear zone around the disc is measured and interpreted against published zone breakpoints. A larger zone is not always a better drug, because diffusion depends on molecular size.

Laboratory sensitivity does not guarantee a cure. Penetration, host immunity and drug toxicity still decide the outcome.

Biofilms are communities of bacteria embedded in a self-made matrix on tissue or devices such as catheters, implants and necrotic bone. Bacteria within are slow-growing, protected from immune cells and far less affected by antibiotics, often needing concentrations many times the standard MIC. Standard tests use free-floating bacteria and so miss this tolerance. Management usually requires removal or debridement of the foreign or dead material, not just a longer drug course.

Combinations and prophylaxis

Single-drug therapy is the default. Combinations are justified for specific reasons:

- Severe infection before the pathogen is known, to widen cover.
- Polymicrobial infection, for example mixed aerobes and anaerobes.
- Synergy, as with a beta-lactam plus an aminoglycoside, or a sulfonamide plus a diaminopyrimidine.
- Delaying resistance, as in tuberculosis in human medicine.

Combinations carry outcomes of *synergy* (greater than the sum), *additivity* or *antagonism*. They also increase toxicity, cost and selection pressure, so they should not be used merely for comfort.

Prophylaxis means giving an antibiotic to prevent infection. It is justified when there is a predictable pathogen, a defined short risk period and proven benefit, for example around certain clean-contaminated or implant surgery, given so that tissue levels are present at the time of contamination. It is not justified as a substitute for hygiene, routine post-operative cover in clean procedures, or to prevent viral disease. Prophylactic or growth-promoting use of antibiotics in herds is a major driver of resistance, and national rules on it change, so check the current notification of the relevant Indian authority.

Finally, follow the stewardship rule: right drug, right dose, right duration, reviewed when culture results return, and stopped when no longer needed. Antibiotics are a shared resource for animal and human health.

Concept cleared

Narrowest effective spectrum
Pick the drug that covers the likely pathogen and no more. Broad spectrum disturbs normal flora and selects resistance widely.

Peak versus time
Concentration-dependent drugs need a high peak relative to MIC; time-dependent drugs need levels above MIC for as long as possible.

In vitro is not in vivo

A susceptible report shows the organism is inhibited in a test, not that the drug reaches the site or that the host will clear the infection.

Biofilm tolerance

Bacteria in biofilms survive concentrations that kill free-floating cells, so source control matters as much as the drug.

Memory aid: Selecting an antibiotic: SPASS

Site of infection, Pathogen likely, Activity (spectrum and killing pattern), Safety in this species, Stewardship and residues. Run through the five before naming a drug.

Compare and contrast

Bactericidal versus bacteriostatic

Feature	Bactericidal	Bacteriostatic
Effect	Kills bacteria	Halts multiplication
Dependence on host defences	Lower	Higher
Typical examples	Beta-lactams, aminoglycosides	Tetracyclines, macrolides (usually)
Preferred when	Immunocompromised, endocarditis, sepsis	Healthy host, localised infection

Concentration-dependent versus time-dependent killing

Feature	Concentration-dependent	Time-dependent
Key driver	High peak relative to MIC	Time above MIC
PK/PD index	Peak/MIC or AUC/MIC	Time above MIC
Post-antibiotic effect	Usually prolonged	Short or absent for most
Examples	Aminoglycosides, fluoroquinolones	Beta-lactams

Species notes

Cattle

Food-producing animal: every choice must consider milk and meat withdrawal and residue rules. Rumen flora can be disturbed by oral antibiotics, so route matters.

Poultry

Flock-level treatment through water or feed makes consistent dosing difficult and favours resistance. Egg residues and withdrawal need attention in layers.

Dogs and cats

Culture is practical and should guide chronic or recurrent infections such as pyoderma and urinary tract infection. Some drug classes are riskier in cats.

Horses

Oral antibiotics can upset hindgut flora and cause colitis, so route and class need care.

Sheep and goats

Small ruminants have few licensed products; extra-label use needs veterinary justification and a cautious withdrawal approach.

Clinical pearls

Self-test: 10 questions

1. Selective toxicity means that a drug:

Antibacterials exploit targets absent or different in host cells.

2. Which is generally a time-dependent antibacterial?

Beta-lactam efficacy tracks time above MIC; aminoglycosides and fluoroquinolones are concentration-dependent.

3. The MIC is best defined as the:

Killing is the MBC, not the MIC.

4. Bactericidal therapy is most preferred in:

When host defences are weak, killing is needed.

5. A drawback of broad-spectrum therapy is:

Broad spectrum disturbs flora and broadens selection pressure.

6. Biofilm infections are difficult to treat mainly because bacteria in them:

Tolerance is a physiological and structural protection.

7. In disc diffusion testing, the result is read from the:

Zone diameter is compared with breakpoints.

8. Which is a legitimate reason for combination therapy?

Combinations need a reason such as spread of cover or synergy.

9. Appropriate prophylaxis is:

Prophylaxis should be targeted and brief.

10. The post-antibiotic effect is usually most notable with:

Concentration-dependent drugs often suppress growth after levels fall.

Key points to revise

1. Selective toxicity means the drug harms bacteria more than the host.
2. Spectrum is the range of organisms a drug acts on; prefer the narrowest that is adequate.
3. Bactericidal drugs kill; bacteriostatic drugs inhibit and need host defences.
4. Concentration-dependent drugs depend on peak to MIC; time-dependent drugs on time above MIC.
5. MIC is the lowest concentration that prevents visible growth and is read against breakpoints.
6. Disc diffusion zone size must be interpreted against standard zone breakpoints.
7. Biofilms are tolerant to antibiotics and usually need source control.
8. Prophylaxis needs a defined risk and a short course; combinations need a clear reason.

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- Ch 2. Sulfonamides and diaminopyrimidines (in this book)
- Ch 3. Beta-lactam antibiotics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- WHO: Antimicrobial resistance fact sheet
- Merck Veterinary Manual: Penicillins
- Merck Veterinary Manual: Cephalosporins and cephamycins

CHAPTER 2 OF 19

Sulfonamides and diaminopyrimidines

Sulfonamides block folate synthesis and diaminopyrimidines block its next step, which is why the combination is synergistic and often bactericidal. The chapter covers resistance, crystalluria, coccidiosis and mastitis uses, and residue concerns.

After this chapter you can

- Explain how sulfonamides and diaminopyrimidines block sequential steps of folate synthesis
- Describe why potentiated sulfonamides show synergy
- Explain the mechanism and prevention of crystalluria
- List uses in coccidiosis and mastitis and the limits of each
- Describe resistance, adverse effects and residue considerations

Why folate is the target

Bacteria and protozoa must make their own folic acid, because they generally cannot take up the finished vitamin. Folate is needed to make thymidine, purines and some amino acids, so without it DNA synthesis stops. Mammals take folate from the diet, so a drug that blocks folate *synthesis* shows **selective toxicity**.

The practical lesson is that these drugs are old, cheap and widely available, which is exactly why they are overused and why resistance is common. Treat them as useful drugs that now need a susceptibility check and a clear indication.

This is the central idea of the chapter: two drug groups block two different steps of the same pathway, and each alone is weak but together they are strong.

Sulfonamides: mechanism and properties

Sulfonamides are structural analogues of **para-aminobenzoic acid (PABA)**. The bacterial enzyme *dihydropteroate synthase* normally joins PABA to a pteridine to form dihydropteroic acid. Sulfonamides compete with PABA for this enzyme and block the step. This is competitive antagonism, so excess PABA, such as that released from pus, necrotic tissue or procaine breakdown, reduces their effect.

Used alone, they are mainly **bacteriostatic**. They have a broad but now unreliable spectrum covering some Gram-positive and Gram-negative bacteria, and some protozoa such as coccidia and Toxoplasma.

The sulfonamide group is large. In practice we sort members by behaviour: *systemic* agents absorbed well and used for infections in tissues, *gut-active* agents that stay in the lumen, and *topical* agents for skin and eye. The behaviour, not the name, tells you the use.

Sulfonamides differ in absorption and excretion. Some are well absorbed and excreted in urine, some are poorly absorbed from the gut and act locally, and some are used topically. They are usually weak acids, widely distributed, and cross into most body fluids including the CSF. Metabolism is mainly by acetylation, with species differences: dogs do not acetylate sulfonamides well, which affects their handling in that species.

Diaminopyrimidines and potentiation

Trimethoprim and related drugs such as ormetoprim and pyrimethamine inhibit **dihydrofolate reductase (DHFR)**, the next enzyme, which converts dihydrofolate to tetrahydrofolate. They are selective because bacterial DHFR is far more sensitive than the mammalian enzyme. Pyrimethamine is used against protozoa.

When a sulfonamide and a diaminopyrimidine are given together, the sequential block makes the effect much greater than either alone: **synergy**, also called potentiation. The combination is often **bactericidal**, has a broader spectrum, and delays resistance. These are called **potentiated sulfonamides**, for example trimethoprim-sulfadiazine and trimethoprim-sulfamethoxazole.

The best synergy occurs when the two components reach the site in an effective ratio, which is a reason to use licensed combinations rather than improvised mixtures. Trimethoprim is lipophilic, widely distributed and a weak base, and it can concentrate in prostate and in tissues, while the sulfonamide partner is a weak acid.

Resistance

Resistance is widespread. Mechanisms include altered dihydropteroate synthase with low affinity for the drug, increased PABA production, and acquired resistant enzymes carried on plasmids. Resistance genes for sulfonamides spread easily and often travel together with those for other classes.

Because resistance is so common, the usual rule is to confirm susceptibility rather than assume it, and to avoid long unsupervised courses in herds or flocks, which select resistant bacteria and resistant coccidia. Mixing feed or water medication also carries a risk of uneven intake by sick animals.

Cross-resistance occurs between members of the sulfonamide group, so a resistant organism is resistant to the whole group. Resistance to trimethoprim arises through resistant DHFR enzymes. The combination retains activity against some organisms resistant to either component, but this advantage is not guaranteed. Bacteria may also bypass the block when pus supplies thymidine, which is another reason these drugs work poorly in abscesses.

Adverse effects and crystalluria

Sulfonamides and their acetylated metabolites may be poorly soluble in acidic urine and can precipitate in the kidney tubules and urinary tract. This is **crystalluria**. It may cause haematuria, tubular damage and obstruction. Risk factors are dehydration, acidic urine, high doses and poorly soluble agents. Prevention is straightforward: keep the animal well hydrated, avoid in dehydrated or oliguric patients, and favour more soluble products or alkaline urine when needed.

Other effects include hypersensitivity reactions, and in dogs, keratoconjunctivitis sicca (dry eye), immune-mediated polyarthritis, and drug fever, particularly with potentiated products, with certain breeds such as Doberman pinschers reported as predisposed. Folate-deficiency effects such as bone marrow suppression can occur with prolonged use or in animals with poor folate status. Trimethoprim combinations may suppress thyroid function in dogs on longer use. Intravenous potentiated sulfonamide given rapidly to horses can cause collapse, so route and rate matter. Cats may be sensitive to some effects.

Uses in coccidiosis and mastitis, and residues

Coccidiosis. Sulfonamides such as sulfaquinoxaline and sulfadimidine act on the asexual stages of *Eimeria*, notably the schizont stage, and work best when given early. Because they are not fully coccidiocidal, host immunity develops while the drug suppresses multiplication. Dosing in water is common in poultry and young ruminants. Whether a sulfonamide is permitted in laying birds varies, and egg residue rules apply; check the current notification.

Mastitis. Sulfonamides and potentiated products have been used for mastitis, mostly by injection. Udder pus and debris blunt their action, resistance is common, and the drug must reach the infected quarter at an effective level, so they are not an automatic first choice. Susceptibility testing and the current label for milk withdrawal guide use. In every case treat mastitis as a herd problem: milking hygiene and dry-cow management matter more than any single drug.

Common confusions. Students often think trimethoprim and sulfonamides compete with each other. They do not: they act on different enzymes in one pathway. Another confusion is that sulfonamides are antimetabolites that harm the host. They do not harm the host folate pathway because the host does not synthesise folate. Finally, *bacteriostatic alone but bactericidal together* is a statement about the combination, not about each component.

Other uses. Potentiated sulfonamides treat a range of respiratory, urinary, enteric and soft-tissue infections and some protozoal infections.

Residues. Sulfonamides are among the residues most often detected in animal products, because of long use and slow clearance at times. Withdrawal periods and maximum residue limits apply; check the current notification and product label for India.

Concept cleared

Sequential block
Sulfonamides stop PABA being used; diaminopyrimidines stop DHFR. Two blocks in one pathway give synergy.

Selective toxicity by dependence

Microbes must synthesise folate while mammals take it from food, so the pathway is safe to attack.

PABA competition

Pus and tissue debris contain PABA and thymidine, weakening the effect of these drugs in abscesses.

Solubility and crystals

Poorly soluble drugs and acidic, concentrated urine lead to crystals, which hydration prevents.

Memory aid: Folate steps: PABA then DHFR

Sulfonamides Stop the first step (PABA to dihydropteroate); Trimethoprim Terminates the Tetrahydrofolate step (DHFR). S for first, T for second.

Compare and contrast

Sulfonamide versus diaminopyrimidine

Feature	Sulfonamide	Diaminopyrimidine
Target enzyme	Dihydropteroate synthase	Dihydrofolate reductase
Mimics	PABA	Folate substrate (inhibitor)
Alone	Bacteriostatic	Bacteriostatic
Examples	Sulfadiazine, sulfadimidine	Trimethoprim, ormetoprim, pyrimethamine

Sulfonamide alone versus potentiated sulfonamide

Feature	Alone	Potentiated
Action	Bacteriostatic	Often bactericidal
Spectrum	Narrower	Broader
Resistance	High	Somewhat delayed
Effect in pus	Poor	Still reduced

Species notes

Dogs

Dry eye, polyarthritis and hypersensitivity are noted with potentiated sulfonamides; dogs acetylate poorly, so crystalluria and effects need monitoring.

Horses

Rapid intravenous potentiated products can cause collapse; oral use can disturb hindgut flora.

Poultry

Used for coccidiosis and some bacterial disease; egg and meat residue rules and toxicity at high water levels are concerns.

Cattle and calves

Used for scours, respiratory disease and coccidiosis; milk and meat withdrawal must be observed.

Cats

May show greater sensitivity to adverse effects; use carefully and with hydration.

Clinical pearls

Self-test: 10 questions

1. Sulfonamides are structural analogues of:

They compete with PABA for dihydropteroate synthase.

2. Trimethoprim inhibits:

DHFR is the second step.

3. Synergy between a sulfonamide and trimethoprim arises from:

Two different steps are blocked.

4. Crystalluria is best prevented by:

Dilute, less acidic urine keeps drugs soluble.

5. Why do sulfonamides work poorly in abscesses?

Debris supplies PABA and thymidine.

6. Sulfonamides in coccidiosis mainly act on the:

They suppress asexual multiplication.

7. A known adverse effect in dogs given potentiated sulfonamides is:

Dry eye is well described.

8. Sulfonamide alone is typically:

Combination with a diaminopyrimidine often becomes bactericidal.

9. Resistance to sulfonamides commonly involves:

Resistant enzymes are plasmid carried.

10. Pyrimethamine is mainly used against:

It is a diaminopyrimidine used for protozoal infection.

Key points to revise

1. Sulfonamides inhibit dihydropteroate synthase by mimicking PABA.
2. Diaminopyrimidines inhibit DHFR.
3. The combination is synergistic and often bactericidal.
4. Folate synthesis is a selective target because mammals use dietary folate.
5. Crystalluria occurs in acidic, concentrated urine with poorly soluble drugs.
6. Resistance is plasmid-mediated and common.
7. Sulfonamides act on early asexual stages of Eimeria.
8. Residues in food are an ongoing concern; check current rules.

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- Ch 3. Beta-lactam antibiotics (in this book)
- Ch 1. Principles of chemotherapy and antibiotic selection (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Sulfonamides
- WHO: Antimicrobial resistance fact sheet
- Merck Veterinary Manual: Penicillins

CHAPTER 3 OF 19

Beta-lactam antibiotics

Beta-lactams block cell wall synthesis and kill growing bacteria. The chapter covers penicillin groups, cephalosporin generations, beta-lactamase inhibitors and why carbapenems are kept for human medicine and reserve use.

After this chapter you can

- Explain how beta-lactams inhibit peptidoglycan cross-linking and why this kills growing bacteria
- Classify penicillins and describe the spectrum of each group
- Describe cephalosporin generations and the trend in spectrum
- Explain how beta-lactamase inhibitors restore activity
- Explain why carbapenems are reserved and the stewardship rationale

Mechanism: attacking the cell wall

The bacterial cell wall is built from **peptidoglycan**, a mesh of sugar chains cross-linked by short peptides. The cross-linking is done by **penicillin-binding proteins (PBPs)**, which are transpeptidase enzymes. Beta-lactams, named for the four-membered beta-lactam ring, mimic the end of the peptide and bind PBPs irreversibly. Cross-linking stops.

The cell keeps growing but the wall is weak. Autolytic enzymes then break the wall and the cell bursts from internal osmotic pressure. This explains three key facts. Beta-lactams are **bactericidal**, they act only on **actively growing** bacteria, and they are **time-dependent** drugs. Mammalian cells have no cell wall, so toxicity to the host is low.

Beta-lactams are weak acids, mostly stay in extracellular fluid, are excreted largely by the kidney through tubular secretion, and do not easily enter cells. Mycoplasma lacks a cell wall and is naturally resistant.

Common confusion: a bacteriostatic drug that stops growth can antagonise a beta-lactam, because the beta-lactam needs growing cells. Also, Gram-negative bacteria have an outer membrane, so a drug must pass porin channels before it reaches PBPs, which is why spectrum differs between members.

Resistance to beta-lactams

There are three main mechanisms.

1. **Beta-lactamases** hydrolyse the ring. This is the commonest mechanism. Gram-positive bacteria release the enzyme outside the cell, and Gram-negative bacteria hold it in the periplasmic space.
2. **Altered PBPs** with low affinity for the drug. The classic example is the *mecA* gene in methicillin-resistant staphylococci, which makes them resistant to practically all beta-lactams except specially designed ones. This is why MRSA and MRSP are a serious problem.
3. **Reduced entry or increased efflux** in Gram-negative bacteria through changes in porin channels.

Extended-spectrum beta-lactamases (ESBLs) and carbapenemases in Gram-negative bacteria are a global concern because they remove many options at once.

Penicillins

All penicillins share the 6-aminopenicillanic acid core. They are grouped by spectrum.

- **Natural penicillins** (benzylpenicillin, penicillin V). Active against Gram-positive organisms, anaerobes and a few Gram-negatives. Destroyed by beta-lactamase. Benzylpenicillin is acid-labile, so oral absorption is poor. Procaine and benzathine forms are depot preparations that give prolonged levels after injection, but they also lead to long residue periods in food animals.
- **Penicillinase-resistant penicillins** (cloxacillin, dicloxacillin, oxacillin). Active against staphylococci that produce beta-lactamase. They are used mainly in mastitis intramammary products. They are not effective against MRSA.
- **Aminopenicillins** (ampicillin, amoxicillin). Wider spectrum including some Gram-negative organisms such as certain *E. coli* and *Salmonella*, but still destroyed by beta-lactamase. Amoxicillin is acid-stable and better absorbed orally than ampicillin. Because these drugs are mostly excreted by the kidney, urine concentrations are high, which suits urinary infection, but dose adjustment thinking is needed in renal failure.
- **Extended-spectrum penicillins** (carboxypenicillins and ureidopenicillins such as ticarcillin and piperacillin). Added *Pseudomonas* activity; used mainly with an inhibitor and mostly in companion animal or hospital practice.

The main toxic problem is **hypersensitivity**, which can be severe, and cross-allergy exists among penicillins and, to a lesser extent, cephalosporins. Oral use can disturb gut flora, notably in rodents, rabbits, guinea pigs and ruminants.

Cephalosporins by generation

Cephalosporins share a cephem nucleus and are more resistant to many staphylococcal beta-lactamases than natural penicillins. They are grouped into **generations**. The pattern is a rough guide, not a rigid rule.

- **First generation** (cefazolin, cephalexin, cefadroxil). Good against Gram-positive cocci including staphylococci, with limited Gram-negative cover. Used for skin infections and surgical prophylaxis. Oral first-generation agents are absorbed well in monogastric animals.
- **Second generation** (cefoxitin, cefuroxime). A little more Gram-negative activity, and cefoxitin (technically a cephamycin) has anaerobe cover.
- **Third generation** (ceftiofur, cefovecin, cefpodoxime, ceftriaxone). Stronger Gram-negative activity and better tissue penetration, with somewhat less Gram-positive activity than first generation. Ceftriaxone and similar drugs reach the CSF.
- **Fourth generation** (cefquinome, cefepime). Broad cover including Gram-positives and many Gram-negatives and some resistance to beta-lactamases.

In general, moving from first to later generations increases Gram-negative activity. Cephalosporins are **not active** against enterococci, and are poor against MRSA. Third and later generations are classed by international bodies among important antimicrobials for human medicine, so use them only when justified, ideally after culture. Check the current Indian policy on their use in animals.

Beta-lactamase inhibitors

Clavulanic acid, sulbactam and tazobactam have little antibacterial activity of their own. They bind beta-lactamases and inactivate them, acting as **suicide inhibitors**. When combined with a penicillin, the partner drug is protected and its spectrum is restored. Amoxicillin-clavulanate is the best-known veterinary example, extending cover to many beta-lactamase-producing staphylococci, *E. coli* and anaerobes.

Inhibitors have limits. They do not help when resistance is due to altered PBPs, as in MRSA, and they do not inactivate all beta-lactamases, such as ESBLs of certain classes. Combination drugs should therefore be used where beta-lactamase producers are genuinely likely, not as a default for every infection. Gastrointestinal upset is a recognised effect.

Remember the logic: an inhibitor combination answers the question *is an enzyme destroying my drug?* It does not answer *is the target changed?* or *is the drug kept out?* When culture shows a plain penicillin-susceptible organism, an inhibitor combination adds spectrum and selection pressure without benefit, and the narrower drug is the better stewardship choice.

Carbapenems and why they are reserved

Carbapenems (imipenem, meropenem, ertapenem) have the widest spectrum of the beta-lactams, covering Gram-positives, Gram-negatives and anaerobes, and are stable against most beta-lactamases including ESBLs. They are usually the last line for serious multi-drug-resistant Gram-negative infections in human hospitals.

They are reserved for these reasons:

- They are among the few options left when ESBL-producing organisms cause severe infection in people.
- Use in animals could select carbapenemase producers, which can spread to humans, and resistance genes are often on mobile elements carrying other resistance too.
- Many authorities restrict or prohibit their use in food animals, and recommend that any companion-animal use be only after culture shows no alternative. Check the current Indian notification and veterinary council guidance.

Stewardship principle: protect drugs that human medicine cannot do without. Even when a species is not a food animal, hospital-acquired resistant bacteria can pass between animals and people, so the same restraint applies to companion animals. Beta-lactam residues in milk also cause allergic reactions and interfere with dairy fermentation, so withdrawal periods must be respected.

Concept cleared

Cell wall as the target

Blocking PBP cross-linking weakens the wall; growing bacteria burst. Hence bactericidal, time-dependent, and inactive on non-dividing cells or cell-wall-less Mycoplasma.

Beta-lactamase protection

Enzymes cut the ring; inhibitors block the enzymes. The inhibitor protects the penicillin, it does not widen the drug beyond enzyme-mediated resistance.

Altered target resistance

MRSA has a PBP with low affinity, so all standard beta-lactams and inhibitor combinations fail.

Reserve drugs

Carbapenems are kept to protect human treatment of resistant Gram-negative infection.

Memory aid: Beta-lactam features: C-T-G

Cell wall target, Time-dependent, Growing cells only. Each point helps answer questions on mode of action and combination logic.

Compare and contrast

Penicillin groups

Group	Examples	Main spectrum	Beta-lactamase stable?
Natural	Benzylpenicillin	Gram-positive, anaerobes	No
Penicillinase-resistant	Cloxacillin	Staphylococci	Yes
Aminopenicillins	Amoxicillin, ampicillin	Plus some Gram-negatives	No (unless with inhibitor)
Extended-spectrum	Piperacillin	Plus Pseudomonas	No (with inhibitor)

Cephalosporin generations

Generation	Examples	Trend
First	Cefazolin, cephalexin	Gram-positive focus
Second	Cefoxitin, cefuroxime	More Gram-negative, anaerobes with cefoxitin
Third	Ceftiofur, cefovecin, ceftriaxone	Strong Gram-negative, CSF entry for some
Fourth	Cefquinome, cefepime	Broad, more enzyme stable

Species notes

Cattle
Intramammary penicillinase-resistant penicillins and cephalosporins are widely used; milk and meat withdrawal and discard of milk must be followed.

Dogs and cats
First-generation cephalosporins and amoxicillin-clavulanate are common for skin and urinary infections; hypersensitivity can occur.

Horses
Procaine penicillin can cause reactions if inadvertently given

Rabbits, guinea pigs, hamsters
Oral penicillins and some cephalosporins can cause fatal

intravenously; oral beta-lactams may disturb hindgut flora.

dysbiosis; avoid unless a specialist advises.

Poultry and pigs
Used in flock and herd treatment; check residue rules and the current policy on cephalosporin use in food animals.

Clinical pearls

Self-test: 10 questions

1. Beta-lactams act by inhibiting:

They bind penicillin-binding proteins.

2. Beta-lactams are ineffective against Mycoplasma because:

No peptidoglycan means no target.

3. Cloxacillin is mainly valued for:

It resists staphylococcal penicillinase.

4. Clavulanic acid works by:

It is a suicide inhibitor of beta-lactamase.

5. MRSA is resistant mainly because of:

A low-affinity PBP makes beta-lactams ineffective.

6. Which pair is correct?

Gram-negative activity rises with generation.

7. Which is the main reason carbapenems are reserved?

Stewardship protects them for human use.

8. Beta-lactams show killing that is:

Time above MIC is the driver.

9. The most important adverse effect class of penicillins is:

Allergic reactions are the main concern.

10. Amoxicillin differs from benzylpenicillin in being:

Aminopenicillins are orally absorbed and broader.

Key points to revise

1. Beta-lactams bind PBPs and block peptidoglycan cross-linking.
2. They are bactericidal and time-dependent and need growing bacteria.
3. Beta-lactamase is the commonest resistance mechanism.
4. mecA gives altered PBP and MRSA, resistant to most beta-lactams.
5. Penicillins are grouped as natural, penicillinase-resistant, amino and extended-spectrum.
6. Gram-negative activity generally rises from first to later cephalosporin generations.
7. Clavulanic acid, sulbactam and tazobactam inhibit beta-lactamases.
8. Carbapenems are reserved for resistant Gram-negative infection and protected for human use.

Go deeper on this site

- Ch 4. Aminoglycosides and aminocyclitols (in this book)
- Ch 2. Sulfonamides and diaminopyrimidines (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Penicillins
- Merck Veterinary Manual: Cephalosporins and cephamycins
- WHO: Antimicrobial resistance fact sheet

CHAPTER 4 OF 19

Aminoglycosides and aminocyclitols

Aminoglycosides are bactericidal, concentration-dependent drugs that act on the 30S ribosome and are used mainly against aerobic Gram-negative bacteria. Their narrow safety margin (kidney, inner ear, neuromuscular junction) and long tissue residues shape every clinical decision.

After this chapter you can

- Explain how aminoglycosides enter bacteria, bind the ribosome and kill
- State the spectrum and why anaerobes are naturally resistant
- Describe the mechanisms and risk factors for nephrotoxicity, ototoxicity and neuromuscular blockade
- Explain why gentamicin, amikacin and streptomycin differ in use and resistance
- Explain why aminoglycoside residues persist in kidney and what this means for withdrawal and stewardship

Chemistry and mechanism of action

Aminoglycosides are polycationic sugars joined to an aminocyclitol ring. Gentamicin, amikacin, tobramycin, kanamycin and neomycin carry a 2-

deoxystreptamine ring. **Streptomycin** carries a streptidine ring, and **spectinomycin** is a related aminocyclitol without amino sugars, which is why it is only bacteriostatic and gentler.

The drug first crosses the outer membrane of Gram-negative bacteria, then is taken across the inner membrane by an **energy-dependent, oxygen-requiring** process driven by the membrane electrical potential. Inside, it binds the **30S ribosomal subunit**, distorts the A site and causes misreading of mRNA. Faulty proteins insert into the cell membrane, make it leaky and allow still more drug to enter. This positive feedback explains why, unlike most protein synthesis inhibitors, aminoglycosides are **bactericidal**.

Killing is **concentration-dependent**, and a **post-antibiotic effect** continues after levels fall. Bacteria also show temporary adaptive resistance after exposure. For these reasons the modern approach favours a high peak followed by a long drug-free interval rather than frequent small exposures. This is a concept, not a dose, and the label or a formulary must be used for the actual regimen.

Spectrum and common confusions

The useful spectrum is aerobic Gram-negative rods (Escherichia coli, Klebsiella, Pseudomonas, Proteus, Salmonella) and some staphylococci. Because uptake needs oxygen, **anaerobes are intrinsically resistant**. The same logic explains poor activity in abscess pus, necrotic tissue and low pH, where oxygen is low and the drug binds to debris. Streptococci and enterococci are only weakly susceptible alone, but a cell-wall active drug such as a penicillin damages the wall and lets aminoglycosides in, giving **synergy**.

Individual agents differ. Gentamicin is the workhorse for Gram-negative sepsis, uterine and ocular uses. Amikacin is a semi-synthetic kanamycin derivative that resists many bacterial inactivating enzymes, so it is kept for gentamicin-resistant organisms and should be protected by restricted use. Streptomycin is used for mycobacteria, Brucella (with a tetracycline) and some Leptospira work, and in veterinary practice it often appears as dihydrostreptomycin. Neomycin is poorly absorbed orally and is used locally in the gut and on skin. Spectinomycin is used in poultry and pigs for Mycoplasma and enteric infections.

A frequent confusion: aminoglycosides are not absorbed from the gut after oral dosing, so they are given by injection for systemic infection. A drug that stays in the gut after oral use is not a failure, it is a feature for enteric infections, but absorption can rise in a damaged intestine.

Pharmacokinetics

Aminoglycosides are highly polar. They distribute mainly in **extracellular fluid**, so the dose reflects lean body weight and fat is not a useful reservoir. Penetration into CSF, bone, prostate and the eye is poor. Protein binding is low. Excretion is by **glomerular filtration** of unchanged drug, so renal disease, dehydration and neonatal immaturity prolong the half-life.

A small fraction is taken up by proximal tubular cells and by hair cells of the inner ear and is released very slowly. This tissue binding explains both toxicity and the long residue persistence described below. Plasma levels can look safe while the kidney cortex is holding a large load.

Nephrotoxicity, ototoxicity and neuromuscular block

Nephrotoxicity. Filtered drug binds to the brush border of proximal tubule cells, is taken in by receptor-mediated endocytosis and concentrates in lysosomes. Lysosomal damage, mitochondrial injury and cell death follow. Early signs are enzymuria and casts, then loss of concentrating ability, and later a rise in creatinine. Injury is often non-oliguric and can be reversible because tubule cells regenerate. Risk rises with dehydration, pre-existing renal disease, older age, sepsis, repeated or prolonged dosing, and combination with other nephrotoxins such as NSAIDs, amphotericin B and loop diuretics. Giving the same total as one large dose reduces uptake because the transport process saturates, which is another reason for the extended-interval approach.

Ototoxicity. The drug accumulates in perilymph and kills sensory hair cells, which do not regenerate. Cochlear damage causes deafness. Vestibular damage causes ataxia, head tilt and nystagmus. Gentamicin and streptomycin tend to affect the vestibular system, whereas neomycin and amikacin are more cochlear. Cats are particularly sensitive to vestibular effects. Loop diuretics add risk. Topical gentamicin or neomycin in a perforated ear drum can reach the inner ear.

Neuromuscular blockade. Aminoglycosides reduce presynaptic acetylcholine release and postsynaptic sensitivity by competing with calcium. The effect is rapid after fast intravenous injection or intraperitoneal instillation and is worse with anaesthetics, muscle relaxants, magnesium and in hypocalcaemia. Calcium salts and neostigmine can partly reverse it. Do not give these drugs as a fast intravenous bolus.

Monitoring means keeping the patient hydrated, checking urine for casts and specific gravity, and avoiding combinations with other nephrotoxic drugs.

Resistance and interactions

The commonest mechanism is **enzymatic modification** by acetyl-, phosphoryl- or adenylyl-transferases, usually plasmid-carried and transferable between species. Each enzyme attacks a defined set of drugs, which is why gentamicin resistance does not always predict amikacin resistance. Other mechanisms are reduced uptake, efflux, and ribosomal methylation by 16S rRNA methyltransferases, which gives high-level resistance to nearly the whole class. Mutation of the ribosomal target is important for streptomycin in single-step resistance, for example in mycobacteria.

An important *in vitro* interaction: carbenicillin and other penicillins can inactivate aminoglycosides if mixed in the same syringe or infusion bag. This is a pharmaceutical incompatibility and differs from the helpful in vivo synergy. Aminoglycosides are also inactivated in acidic or high-salt, high-divalent-cation environments, and they are less active in pus.

Residues, withdrawal and stewardship

Because kidney tissue retains aminoglycosides for a long time, residues can be found in kidney and, to a lesser extent, liver long after plasma levels disappear. **Withdrawal times are therefore long** and kidney is usually the limiting tissue in meat. Withdrawal is also longer in animals with renal damage. For these reasons, extra-label use in food animals is hazardous. Milk residues occur after intramammary or parenteral use, and the licensed withdrawal for milk must be respected. Maximum residue limits and the list of permitted products in India are set by national authorities. Check the current notification from FSSAI and the relevant veterinary authority before applying any figure.

Stewardship points: aminoglycosides are valuable against multidrug-resistant Gram-negatives, and amikacin in particular is a reserve drug. Use culture and sensitivity, avoid prophylactic or routine use, avoid sub-therapeutic exposure that selects resistance, and follow national and WOAH or WHO guidance on categories of importance. In human medicine streptomycin and amikacin are important for tuberculosis and resistant infections, so animal use should be restricted accordingly.

Concept cleared

Oxygen-dependent entry
Aminoglycosides need an energised, oxygenated bacterial membrane to enter, so anaerobes and bacteria in necrotic, low-oxygen, acidic pus are poorly affected.

Concentration-dependent killing
Higher peak relative to MIC gives faster kill and a post-antibiotic effect, so a large dose with a long interval is both effective and less toxic than frequent small doses.

Tissue trapping
Uptake into proximal tubule cells and inner-ear hair cells explains toxicity and long residues even when plasma levels are low.

Synergy with cell-wall drugs
Penicillins damage the wall and allow aminoglycosides into Gram-positive cells, giving synergy that is helpful in vivo but must not be mixed in one syringe.

Memory aid: Aminoglycoside cautions: NOW
Nephro, Oto, neuromuscular Weakness. Also remember they are Ineffective without Oxygen, so anaerobes escape.

Compare and contrast

Aminoglycosides compared

Drug	Main use	Resistance point	Key caution
Gentamicin	Gram-negative sepsis, local ocular and uterine use	Common modifying enzymes	Nephrotoxic, vestibular
Amikacin	Gentamicin-resistant Gram-negatives	Resists many enzymes, ribosomal methylases	Reserve drug, nephrotoxic
Streptomycin / dihydrostreptomycin	Mycobacteria, Brucella with tetracycline, Leptospira	Single-step ribosomal mutation	Vestibular and cochlear damage, esp. cats
Neomycin	Oral gut or topical use	Modifying enzymes	Not for systemic use, toxic if absorbed
Spectinomycin	Poultry and pig Mycoplasma and enteric infections	Ribosomal mutation, enzymes	Mainly bacteriostatic, less toxic

Toxicity of aminoglycosides

Target	Mechanism	Reversible?	Risk modifiers
Kidney	Proximal tubule uptake, lysosomal injury	Often yes	Dehydration, NSAIDs, age, sepsis
Cochlea	Hair cell death	No	Loop diuretics, long courses
Vestibular system	Hair cell death	Partly by compensation	Cats, streptomycin and gentamicin
Neuromuscular junction	Reduced ACh release, calcium competition	Yes with calcium, neostigmine	Anaesthetics, fast IV, low calcium

Species notes

Cattle

Very long kidney withdrawal and milk residue concerns. Extra-label use is risky, so rely on the label and the current national rules.

Dogs

Nephrotoxicity is the main concern, especially in dehydrated or older dogs and with concurrent NSAIDs. Keep the patient hydrated.

Cats

Prone to vestibular toxicity, particularly with streptomycin and dihydrostreptomycin. Use with great care.

Horses

Gentamicin and amikacin are used for Gram-negative infections, including intra-articular and regional perfusion. Monitor kidney, and note risk with NSAIDs and in foals with sepsis.

Poultry and pigs

Neomycin, apramycin, spectinomycin and others are used for gut infections. Check current approvals and withdrawal periods for each product.

Clinical pearls

Self-test: 10 questions

1. Why are anaerobic bacteria intrinsically resistant to aminoglycosides?

Entry is an oxygen-dependent, energy-driven process, so anaerobes do not take up the drug.

2. Which ribosomal subunit do aminoglycosides bind?

They bind the 30S subunit and cause mRNA misreading.

3. Which statement about killing pattern is correct?

High peaks give greater kill, and the effect persists after levels fall.

4. Which factor most increases the risk of nephrotoxicity?

Reduced renal perfusion and other nephrotoxins increase tubular accumulation and injury.

5. Ototoxicity of aminoglycosides is mainly caused by:

Drug accumulates in perilymph and destroys sensory hair cells, which do not regenerate.

6. Aminoglycoside-induced neuromuscular weakness is best treated with:

Calcium opposes the reduced acetylcholine release.

7. Why is amikacin kept for resistant Gram-negative infections?

Its structure protects it from many enzymes, so it should be preserved as a reserve drug.

8. Which tissue most often determines the withdrawal time of aminoglycosides in food animals?

Kidney retains the drug for a long time after plasma levels fall.

9. Which species is especially prone to vestibular toxicity from streptomycin?

Cats are particularly sensitive to vestibular effects of this group.

10. The synergy between a penicillin and an aminoglycoside against streptococci depends on:

Wall damage allows more aminoglycoside inside. Mixing in a syringe inactivates the aminoglycoside.

Key points to revise

1. Aminoglycosides bind the 30S subunit and are bactericidal.
2. Uptake needs oxygen, so anaerobes are resistant.
3. Killing is concentration-dependent with a post-antibiotic effect.
4. They are not absorbed from the gut and reach mainly extracellular fluid.
5. Excretion is by glomerular filtration, and renal failure prolongs half-life.
6. Toxicities are nephrotoxicity, ototoxicity and neuromuscular blockade.
7. Resistance is mainly by plasmid-borne modifying enzymes, and amikacin resists many of them.
8. Residues persist in kidney, so withdrawal times are long and national limits must be checked.

Go deeper on this site

- Ch 5. Tetracyclines and phenicols (in this book)
- Ch 3. Beta-lactam antibiotics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- FDA Center for Veterinary Medicine: Judicious use of antimicrobials
- FDA Animal Antibiotic Stewardship Plan
- WHO Antimicrobial resistance fact sheet

CHAPTER 5 OF 19

Tetracyclines and phenicols

Tetracyclines and phenicols are broad-spectrum, mainly bacteriostatic protein synthesis inhibitors. This chapter explains how they act, why they chelate calcium, how resistance spreads, and why chloramphenicol is restricted while florfenicol is used in food animals.

After this chapter you can

- Describe the ribosomal targets and bacteriostatic action of tetracyclines and phenicols
- Explain the spectrum, including intracellular and vector-borne pathogens
- Explain calcium chelation and its effects on absorption, teeth and intravenous safety
- Compare oxytetracycline and doxycycline
- Explain chloramphenicol hazards, why florfenicol differs, and the main resistance mechanisms

Tetracyclines: mechanism and spectrum

Tetracyclines have a four-ring structure. They enter bacteria by passive diffusion through porins and by an energy-dependent transport, and bind the **30S ribosomal subunit**. There they block the A site so that aminoacyl-tRNA cannot attach, and protein synthesis stops. The effect is **bacteriostatic**, so host defences must clear the organism.

The spectrum is broad. It includes many Gram-positive and Gram-negative bacteria, but the clinical value today lies mainly in organisms that live inside cells or need special handling: *Rickettsia*, *Anaplasma*, *Ehrlichia*, *Chlamydia*, *Mycoplasma*, *Borrelia*, *Brucella* and *Leptospira*. Their good tissue and cell penetration help here. Because resistance is now widespread among common enteric and respiratory bacteria, tetracyclines should not be chosen blindly for these infections.

Tetracyclines also affect mammalian mitochondrial ribosomes slightly and have non-antibacterial effects such as matrix metalloproteinase inhibition and anti-inflammatory activity. These are the basis for some uses of doxycycline in skin and periodontal disease, but they are secondary to the antibacterial action.

Calcium chelation and its consequences

Tetracyclines bind divalent and trivalent cations (calcium, magnesium, iron, aluminium and zinc). This single chemical property explains several clinical points.

- **Absorption.** Oral tetracycline given with milk, antacids, iron or mineral supplements forms insoluble chelates and absorption falls. Doxycycline is less affected because it is more lipophilic.
- **Teeth and bone.** The drug deposits in developing teeth and growing bone as a calcium complex, causing yellow-brown discolouration and sometimes enamel hypoplasia. It is avoided in pregnant animals and in the young during tooth development unless the benefit is clear.
- **Intravenous safety.** Rapid intravenous injection binds plasma calcium and can cause hypotension, collapse and arrhythmia, particularly in cattle. Injection should be slow and, for some products, diluted, as the label requires.
- **Intramuscular depots.** Long-acting oxytetracycline products are irritant. They can cause painful swelling, tissue damage and a persistent injection-site residue that spoils meat.

A common confusion: chelation is one chemical property with several different clinical faces. In the gut it lowers absorption, in the plasma it can depress the heart if given fast, and in growing tissues it leaves a permanent stain. None of these is a therapeutic benefit.

Pharmacokinetics: oxytetracycline versus doxycycline

Oxytetracycline is the classic veterinary tetracycline. It is usually given by injection to food animals, and oral absorption in ruminants is poor and may disturb rumen flora. It is excreted largely unchanged by the kidney, and also in bile. Long-acting forms prolong exposure but also prolong residues.

Doxycycline is more lipophilic. It is well absorbed orally in monogastric animals, has better tissue and intracellular penetration, a longer half-life, and is eliminated mainly by non-renal routes (bile and gut), so it is safer in renal disease. Its important adverse effect in cats is **oesophageal injury and stricture** if a dry tablet or capsule lodges in the oesophagus. Give tablets followed by water or a small amount of food. In horses, oral doxycycline has been used but the intestinal flora can be disturbed.

Doxycycline is also the common choice for canine ehrlichiosis, anaplasmosis, leptospirosis and some Chlamydia and Mycoplasma infections in companion animals.

Minocycline, a related lipophilic tetracycline, is occasionally used in small animals, and tigecycline-type newer agents are reserved for human medicine. Dosing for every agent must come from the product label or a current formulary, since absorption and tissue binding differ between drugs and species.

Tetracycline adverse effects

Beyond teeth, chelation and injection-site reactions, important adverse effects include gastrointestinal upset, **antibiotic-associated colitis in horses** (disruption of hindgut flora), hepatotoxicity at high doses, photosensitisation, and renal tubular injury with out-of-date or degraded tetracycline, which produces a Fanconi-like syndrome. Tetracyclines can worsen azotaemia through their anti-anabolic effect, and some forms are nephrotoxic in dehydrated animals. Intravenous overdose and some solvent vehicles can cause cardiac depression. Rapid IV injection in cattle is the best-known acute risk.

Phenicols: chloramphenicol and florfenicol

Phenicols bind the **50S subunit** at the peptidyl transferase centre and block peptide bond formation. They are broad-spectrum and mainly bacteriostatic, with activity against many anaerobes, Gram-positive and Gram-negative bacteria and intracellular organisms, and good penetration into CSF, eye and brain.

Chloramphenicol cautions. It has two types of bone marrow toxicity: a dose-related, reversible suppression of erythroid, myeloid and platelet precursors, and a rare idiosyncratic aplastic anaemia described in humans, which is unrelated to dose and can be fatal. Because of the human hazard, it is **prohibited in food-producing animals** in many countries, and Indian rules should be confirmed from the current notification. People handling it should avoid contact and wear gloves. Cats metabolise it slowly because glucuronidation is poor, so dosing intervals must be longer and toxicity is more likely. Neonates share this weakness. It inhibits hepatic cytochrome P450 enzymes and prolongs the effect of drugs such as phenobarbital and some anaesthetics.

Florfenicol is a fluorinated derivative of thiamphenicol. It lacks the nitro group linked to human aplastic anaemia and is not inactivated by the acetyltransferase that destroys chloramphenicol. It is licensed in some countries for respiratory disease in cattle and pigs and for fish. It can still cause reversible dose-related marrow effects, gastrointestinal upset, injection-site lesions and a long tissue withdrawal. Check the label and current rules for milk, dairy cows and calves.

Resistance and stewardship

Tetracycline resistance is commonly by **efflux pumps** encoded by tet genes, or by **ribosomal protection proteins** that dislodge the drug. A third mechanism is enzymatic inactivation. These genes sit on plasmids and transposons and spread between species, so a bacterium resistant to oxytetracycline is often cross-resistant to other older tetracyclines, though doxycycline and minocycline may sometimes remain active. Because older uses were widespread, resistance in farm bacteria is high.

Phenicol resistance includes chloramphenicol acetyltransferase (cat genes), efflux pumps (for example floR, which affects both chloramphenicol and florfenicol) and the *cfr* gene, which methylates 23S rRNA and gives combined resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A. This is why florfenicol use is of concern for linezolid-related resistance.

Stewardship points: do not use tetracyclines for viral diarrhoea or as routine feed additives, avoid prophylaxis, and use culture where possible. The use of antimicrobial growth promoters has been restricted in many countries. Check the current Indian notifications about permitted use and about chloramphenicol, and follow national policy for residues and MRLs.

Concept cleared

Bacteriostatic does not mean weak

Both classes stop protein synthesis without killing directly, but with a competent immune system, they cure many infections. They are poor choices in severely immunocompromised animals.

Chelation

Binding of calcium and other cations explains reduced oral absorption, tooth staining, IV hypotension and cautions with dairy and minerals.

Lipophilicity

Doxycycline's lipophilicity gives better absorption, intracellular penetration and non-renal clearance than oxytetracycline.

Structure explains safety

Florfenicol lacks the nitro group of chloramphenicol and is not destroyed by acetyltransferase, which is why it is used in food animals while chloramphenicol is not.

Memory aid: Tetracycline cautions: TEETH CA

Teeth staining, Esophageal stricture (doxy in cats), Entry with calcium lowers absorption, Tissue irritation at injection, Hypotension if IV fast, Colitis in horses, Azotaemia and nephrotoxicity.

Compare and contrast

Oxytetracycline versus doxycycline

Feature	Oxytetracycline	Doxycycline
Lipophilicity	Lower	Higher
Effect of cations on oral absorption	Marked	Smaller
Main elimination	Kidney and bile	Mostly non-renal
Use in renal disease	More caution	Preferred of the two
Typical use	Food animal injectables	Companion animals, vector-borne disease
Special hazard	Injection-site residue, IV collapse	Oesophageal stricture in cats

Chloramphenicol versus florfenicol

Feature	Chloramphenicol	Florfenicol
Nitro group	Present	Replaced by fluorine
Aplastic anaemia link in humans	Yes, rare	Not reported
Inactivation by acetyltransferase	Yes	No
Food animal use	Prohibited in many countries	Licensed for some food species
Cats	Slow glucuronidation, caution	Not a main concern

Species notes

Cattle

Oxytetracycline long-acting injections cause injection-site residues and lesions. Rapid IV injection can cause collapse. Florfenicol is licensed in some countries for respiratory disease but has restrictions in dairy cows.

Cats

Doxycycline tablets can cause oesophageal stricture if given dry. Chloramphenicol is cleared slowly, so intervals must be longer.

Dogs

Doxycycline is the common choice for ehrlichiosis, leptospirosis and some respiratory pathogens. Chloramphenicol is used cautiously because of marrow effects.

Horses

Tetracyclines can cause enterocolitis. Chloramphenicol is rarely used in food-producing horses, and its status should be checked locally.

Fish and poultry

Oxytetracycline and florfenicol are used in aquaculture and poultry in

some countries, so withdrawal and national limits must be checked.

Clinical pearls

Self-test: 10 questions

1. Which ribosomal subunit do tetracyclines bind?

They block the A site on the 30S subunit.

2. Which statement about phenicols is correct?

They block peptide bond formation at the peptidyl transferase centre.

3. Why should oral tetracycline not be given with antacids or milk?

Divalent and trivalent cations bind the drug.

4. A recognised hazard of dry doxycycline tablets in cats is:

Tablets can lodge in the oesophagus and cause injury, so follow with water or food.

5. Rapid intravenous oxytetracycline in cattle may cause:

Chelation of plasma calcium depresses the heart.

6. Why is doxycycline safer than oxytetracycline in renal disease?

Biliary and intestinal elimination reduce dependence on the kidney.

7. Why is florfenicol acceptable in some food animals when chloramphenicol is not?

Structural differences remove the human aplastic anaemia concern, though residue rules still apply.

8. Why is chloramphenicol more toxic in cats?

Slow glucuronide conjugation prolongs the half-life.

9. Which gene can give combined resistance to phenicols, lincosamides and pleuromutilins?

cfr methylates 23S rRNA, affecting several 50S-binding classes.

10. The commonest tetracycline resistance mechanisms are:

tet genes encode efflux pumps and ribosomal protection proteins.

Key points to revise

1. Tetracyclines bind the 30S subunit and block aminoacyl-tRNA attachment.
2. Phenicols bind the 50S subunit and inhibit peptidyl transferase.
3. Both classes are mainly bacteriostatic and broad spectrum.
4. Tetracyclines chelate calcium, magnesium, iron and aluminium.
5. Chelation explains tooth staining, reduced absorption and IV hypotension.
6. Doxycycline is lipophilic, with non-renal elimination.
7. Chloramphenicol can cause marrow toxicity and human aplastic anaemia, and is banned in food animals in many countries.
8. Tetracycline resistance is by efflux and ribosomal protection, and phenicol resistance includes floR and cfr.

Go deeper on this site

- Ch 6. Macrolides, lincosamides and pleuromutilins (in this book)
- Ch 4. Aminoglycosides and aminocyclitols (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- FDA Center for Veterinary Medicine: Judicious use of antimicrobials
- FDA Animal Antibiotic Stewardship Plan
- WHO Antimicrobial resistance fact sheet

CHAPTER 6 OF 19

Macrolides, lincosamides and pleuromutilins

These three classes bind the 50S ribosomal subunit at overlapping sites and are mainly bacteriostatic. The chapter covers spectrum, tissue concentration, shared resistance, important drug interactions and the serious species-specific toxicities that every veterinary student must know.

After this chapter you can

- Describe how macrolides, lincosamides and pleuromutilins inhibit the 50S ribosome
- Explain the spectrum and tissue distribution of erythromycin, tylosin, clindamycin and tiamulin
- Explain MLS-B cross-resistance and the cfr mechanism
- Identify the main drug interactions, including tiamulin with ionophores
- Recall species-specific toxicities such as lincosamide enterocolitis and tilmicosin cardiotoxicity

Mechanism of action

All three classes bind the **50S ribosomal subunit** near the peptidyl transferase centre, but at slightly different positions.

- **Macrolides** (erythromycin, tylosin, tilmicosin, tulathromycin, gamithromycin) sit in the nascent peptide exit tunnel of the 23S rRNA. They block the growing peptide chain and cause premature release of incomplete peptides.
- **Lincosamides** (lincomycin, clindamycin, pirlimycin) bind at the peptidyl transferase region and interfere with peptide bond formation and tRNA positioning.
- **Pleuromutilins** (tiamulin, valnemulin) bind the peptidyl transferase centre and distort the site where the tRNA is placed, preventing peptide bond formation.

Effects are mainly **bacteriostatic**, though high concentrations can be bactericidal against some organisms. Because the binding sites overlap, a macrolide and a lincosamide given together can compete and lose activity, so the combination is not rational unless a product is specifically licensed for it.

Macrolides: spectrum and pharmacology

Macrolides are active against Gram-positive cocci, *Mycoplasma*, *Campylobacter*, *Lawsonia*, *Rhodococcus* (with rifampin), and respiratory pathogens such as *Pasteurella* and *Mannheimia* for the newer agents. Most Enterobacteriaceae are resistant because the drug does not cross their outer membrane well.

They are lipophilic weak bases. In acidic compartments they become ionised and trapped, a process called **ion trapping**, so tissue and intracellular levels, especially in lung and phagocytes, far exceed plasma levels. White cells carry the drug to the infection site. This explains why newer long-acting macrolides such as tulathromycin give prolonged lung exposure after a single injection, and why plasma levels are a poor guide to efficacy. Milk, being slightly more acidic than plasma, also concentrates the drug, which affects milk withdrawal.

Erythromycin is also a **motilin receptor agonist**, which explains its gastrointestinal prokinetic effect and its tendency to cause cramping, diarrhoea or vomiting. It is also a potent inhibitor of CYP3A and of P-glycoprotein. Tylosin is used widely in pigs and poultry for mycoplasmal and enteric disease and in dogs for chronic colitis. Tilmicosin and tulathromycin are used mainly for bovine and swine respiratory disease.

Lincosamides and pleuromutilins

Lincomycin and clindamycin are active against Gram-positive cocci, many **anaerobes**, *Toxoplasma*, *Mycoplasma* and some protozoa. Gram-negative aerobes are resistant. Clindamycin is better absorbed and more potent than lincomycin. Both penetrate **bone, abscesses and tissues** well and are concentrated in phagocytes, which is why clindamycin is a common choice in dental disease, osteomyelitis and deep skin infection in dogs and cats. They do not cross the blood-brain barrier well in the absence of inflammation.

Elimination is mostly hepatic, with partial biliary and renal excretion. Lincosamides can cause a mild neuromuscular blocking effect, so caution with anaesthetics and relaxants is sensible. In cats, clindamycin capsules can cause oesophagitis if not washed down. Rapid intravenous injection should be avoided because of cardiovascular depression.

Tiamulin and valnemulin are used almost exclusively in pigs and poultry. Their spectrum covers *Mycoplasma*, *Brachyspira* (swine dysentery and spirochaetal colitis), *Lawsonia*, *Actinobacillus pleuropneumoniae* and many Gram-positive bacteria and anaerobes. They accumulate in lung tissue. Resistance develops by stepwise ribosomal mutation, and for Brachyspira this is an important concern. Because pleuromutilins are used in animals but not widely as first-line in people, they are regarded as valuable for animal health. Rules on their use should be checked in the current national notification.

Resistance mechanisms

The key mechanism is methylation of 23S rRNA by **Erm methylases**, which blocks all three drug groups at once and gives the **MLS-B phenotype** (macrolide, lincosamide and streptogramin B). It can be constitutive or **inducible**. In inducible resistance, only a macrolide switches on the gene, so a bacterium may appear sensitive to clindamycin in routine testing but fail in treatment. Laboratories detect this by placing erythromycin and clindamycin discs close together, and a flattened inhibition zone (the D-test) shows induction.

Other mechanisms are efflux pumps (mef, msr), which affect macrolides but not lincosamides, drug inactivation by esterases and phosphotransferases, and ribosomal mutation. The cfr gene gives broad cross-resistance across phenicols, lincosamides, pleuromutilins, oxazolidinones and streptogramin A. Any macrolide use in a herd can therefore select resistance to lincosamides and vice versa.

Interactions and species toxicities

Lincosamides in the wrong species. Lincosamides and, to a lesser extent, macrolides given orally to rabbits, guinea pigs, hamsters, horses and ruminants can wipe out protective gut flora and allow overgrowth of *Clostridium* species, causing fatal enterocolitis. Use is avoided in these species. In dogs and cats diarrhoea is milder.

Erythromycin in horses. In foals it is used for *Rhodococcus equi* pneumonia, but may cause hyperthermia and diarrhoea, and in adults it risks severe colitis. Mares can pass it through milk to foals. Foals receiving macrolides need temperature monitoring in hot weather.

Tilmicosin. It is cardiotoxic. Injection in pigs can be fatal, and it should not be given intravenously. Accidental self-injection in humans has caused deaths. It is also dangerous in horses and goats. Handle with extreme care and check the label.

Tiamulin and ionophores. Tiamulin inhibits hepatic cytochrome P450 and slows metabolism of monensin, salinomycin and narasin. This produces ionophore toxicity (muscle damage, ataxia, paralysis, growth depression and death) even at normal ionophore intake. The two should not be given together, and a withdrawal gap is required by the label. Horses are very sensitive to ionophores.

Other interactions. Erythromycin and some other macrolides inhibit CYP3A and P-glycoprotein and can raise levels of drugs such as cyclosporine, digoxin, theophylline and some opioids. Lincosamides add to neuromuscular blockade of anaesthetics and aminoglycosides.

Residues and stewardship

Macrolides concentrate in tissues and milk, and tulathromycin and tilmicosin persist in lung and fat, which gives long withdrawal periods in some labels. Tiamulin has a withdrawal in pig meat. Always apply the labelled withdrawal and consult the current FSSAI and veterinary authority notifications for Indian MRLs and permitted products.

Stewardship points: reserve newer long-acting macrolides for confirmed or high-risk respiratory disease rather than blanket group treatment. Do not use lincosamides or macrolides in species at risk of fatal enterocolitis. Culture and test for inducible resistance where relevant. Macrolides are also critically important in

human medicine, so veterinary use should follow national and WHO or WOAH advice.

Remember that residue behaviour depends on the product, route and species, so a withdrawal period learned for one macrolide cannot be transferred to another.

Concept cleared

Overlapping binding sites
Macrolides, lincosamides and pleuromutilins all bind near the peptidyl transferase region of the 50S subunit, so they compete with each other and share resistance mechanisms.

Ion trapping
Weakly basic macrolides concentrate in acidic tissues, lung and phagocytes, so tissue concentrations are much higher than plasma concentrations.

Inducible MLS-B resistance
Erm methylase can be switched on by a macrolide, so a clindamycin-susceptible isolate may fail. The D-test detects it.

Enzyme inhibition drives toxicity
Erythromycin and tiamulin inhibit hepatic enzymes, so partner drugs such as ionophores or cyclosporine accumulate.

Memory aid: MLS and friends share a site
Macrolide, Lincosamide, Streptogramin B and pleuromutilin all sit on the same 50S region: one methylase, many problems. Remember D for D-test and Diarrhoea (lincosamides in rabbits and horses).

Compare and contrast

Three 50S-binding classes

Class	Examples	Main spectrum	Key caution
Macrolides	Erythromycin, tylosin, tilmicosin, tulathromycin	Gram-positive, Mycoplasma, Pasteurella, Lawsonia	Tilmicosin cardiotoxicity, GI upset, colitis in horses
Lincosamides	Lincomycin, clindamycin, pirlimycin	Gram-positive, anaerobes, Toxoplasma	Fatal enterocolitis in rabbits, rodents, horses, ruminants
Pleuromutilins	Tiamulin, valnemulin	Mycoplasma, Brachyspira, Lawsonia	Ionophore toxicity

Resistance mechanisms

Mechanism	Macrolides	Lincosamides	Pleuromutilins
erm methylation (MLS-B)	Resistant	Resistant	Usually not the main route
Efflux (mef, msr)	Resistant	Usually susceptible	Not the main route
Ribosomal mutation	Possible	Possible	Stepwise, important in Brachyspira
cfr methylation	Not the main route	Resistant	Resistant

Species notes

Rabbits, guinea pigs, hamsters

Lincosamides and many macrolides given orally can cause fatal clostridial enterocolitis. Avoid.

Horses and foals

Erythromycin or newer macrolides are used for Rhodococcus equi in foals with a risk of hyperthermia and diarrhoea. Lincosamides are dangerous in adults. Horses are also very sensitive to ionophores.

Pigs

Cattle and small ruminants

Tylosin, lincomycin, tiamulin and tilmicosin are used for enteric and respiratory disease. Tilmicosin injection can be fatal. Do not combine tiamulin with ionophores.

Tulathromycin, tilmicosin and gamithromycin are used for respiratory disease. Oral lincosamides are dangerous in ruminants. Tilmicosin is hazardous to goats and humans on self-injection.

Dogs and cats

Clindamycin is used for dental, bone and skin infection and toxoplasmosis. Give capsules to cats with water to avoid oesophagitis. Tylosin is used for chronic colitis in dogs.

Clinical pearls

Self-test: 10 questions

1. Which ribosomal subunit do macrolides bind?

They bind the 23S rRNA of the 50S subunit in the peptide exit tunnel.

2. Why do macrolide concentrations in lung exceed plasma levels?

Ion trapping concentrates lipophilic weak bases in acidic tissues and cells.

3. What is the clinical importance of inducible MLS-B resistance?

A macrolide can induce erm expression, which the D-test detects.

4. Which action of erythromycin explains its prokinetic effect?

Erythromycin mimics motilin and stimulates gastric and intestinal motility.

5. Which species is at greatest risk of fatal enterocolitis from oral lincosamides?

Rabbits and other hindgut fermenters lose protective flora and develop Clostridium overgrowth.

6. Which macrolide is notably cardiotoxic and dangerous on accidental human self-injection?

Tilmicosin has caused fatal cardiac effects, so extreme care is required.

7. Tiamulin combined with monensin leads to:

Tiamulin inhibits hepatic CYP enzymes and raises ionophore exposure.

8. Which drug group is a good choice for Brachyspira hyodysenteriae in pigs?

Tiamulin and valnemulin are important for swine dysentery, though resistance should be monitored.

9. Why is combining a macrolide with a lincosamide generally irrational?

Both bind close sites on the 50S subunit, so one can reduce the effect of the other.

10. In cats, clindamycin capsules should be followed by water to avoid:

Capsules can lodge in the oesophagus and cause local injury.

Key points to revise

1. Macrolides, lincosamides and pleuromutilins bind the 50S subunit and are mainly bacteriostatic.
2. Macrolides concentrate in lung, phagocytes and milk by ion trapping.
3. Erythromycin is a motilin agonist and a CYP3A and P-glycoprotein inhibitor.
4. Clindamycin has good anaerobic, bone and Toxoplasma activity.
5. Tiamulin and valnemulin are used for Brachyspira, Mycoplasma and Lawsonia in pigs and poultry.
6. Erm methylation gives MLS-B cross-resistance and can be inducible.
7. Lincosamides and some macrolides can cause fatal enterocolitis in sensitive species.
8. Tilmicosin is cardiotoxic, and tiamulin with ionophores causes toxicity.

Go deeper on this site

- Ch 7. Fluoroquinolones and other synthetic antibacterials (in this book)
- Ch 5. Tetracyclines and phenicols (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- FDA Center for Veterinary Medicine: Judicious use of antimicrobials
- FDA Animal Antibiotic Stewardship Plan
- WHO Antimicrobial resistance fact sheet

CHAPTER 7 OF 19

Fluoroquinolones and other synthetic antibacterials

How fluoroquinolones such as enrofloxacin and marbofloxacin kill bacteria by blocking DNA gyrase and topoisomerase IV, why they must be used sparingly, and how nitroimidazoles and nitrofurans differ. The chapter stresses spectrum, resistance, residue concerns and responsible use.

> **After this chapter you can**

- Explain how fluoroquinolones block DNA gyrase and topoisomerase IV and why killing is concentration-dependent
- Describe the spectrum, main adverse effects and key interactions of enrofloxacin and marbofloxacin
- Explain how resistance to fluoroquinolones arises and why it spreads easily
- Describe the mechanism, spectrum and cautions for nitroimidazoles and nitrofurans
- Apply the principles of responsible use of critically important antibacterials in practice

Where these drugs fit

Fluoroquinolones, nitroimidazoles and nitrofurans are **synthetic** antibacterials. They are made in the laboratory, not derived from moulds or soil bacteria like penicillins or tetracyclines. Because they have no natural parent molecule, bacteria had less prior exposure to them, but resistance has still appeared quickly once they were widely used.

The three groups have little in common except origin. Fluoroquinolones are broad-spectrum drugs for aerobic bacteria. Nitroimidazoles are mainly for anaerobic bacteria and protozoa. Nitrofurans are older drugs now largely withdrawn from food animal use. Keep these three mechanisms separate in your mind and the chapter becomes simple.

Fluoroquinolone mechanism and spectrum

DNA in a bacterial cell is tightly coiled. To copy or read it, the cell must cut, unwind and rejoin the strands. Two enzymes do this work: **DNA gyrase** (topoisomerase II) and **topoisomerase IV**. Fluoroquinolones lock these enzymes onto the DNA after the strand has been cut. The cut cannot be sealed, DNA breaks accumulate and the cell dies. This is why the drugs are **bactericidal**.

In Gram-negative bacteria the main target is gyrase. In Gram-positive bacteria it is mainly topoisomerase IV. Mammalian topoisomerases are different enough that the drugs are selectively toxic, though not perfectly.

Killing is **concentration-dependent**. The higher the peak concentration relative to the MIC, the faster and more complete the kill, and the drugs also show a useful post-antibiotic effect. This is why the aim is a high peak at an appropriate interval, not frequent small exposures.

The spectrum covers many Gram-negative rods (E. coli, Salmonella, Pasteurella, Pseudomonas to a variable degree), Mycoplasma, and some Gram-positive cocci. Activity against **anaerobes is poor**, so these drugs are not a stand-alone choice for deep abscesses or mixed infections with anaerobes. Newer veterinary agents differ in how well they cover Gram-positives, so check the product literature.

Enrofloxacin and marbofloxacin in practice

Both drugs are well absorbed after oral and parenteral use, distribute widely and reach high levels in tissues such as prostate, lung, bone and skin, and are lipid-soluble enough to penetrate cells. This helps against intracellular organisms.

A frequent point of confusion: **enrofloxacin is partly de-ethylated in the liver to ciprofloxacin**, which is itself active. Marbofloxacin is not handled this way. When you read a susceptibility report, remember that the parent drug and its active metabolite both contribute to the effect.

Important adverse effects and cautions:

- **Cartilage damage in young, rapidly growing animals.** Joint erosions are well recognised in puppies, so these drugs are generally avoided during the growth period. Large breeds are most at risk.
- **Retinal toxicity in cats** linked to enrofloxacin at high exposure, which can cause blindness. This is the reason for strict dose limits on the label.
- **Lowered seizure threshold.** Use caution in epileptic animals.
- **Chelation.** Divalent and trivalent cations (calcium, magnesium, iron, aluminium, zinc) bind the drug in the gut and reduce absorption. Do not mix with antacids, mineral supplements or dairy at the same time.
- Gastrointestinal upset, and local tissue reaction after injection.

Fluoroquinolones can also raise theophylline levels by reducing its clearance, a useful example of a metabolic interaction.

Resistance and responsible use

Fluoroquinolone resistance is built up in steps. **Point mutations** in the genes for gyrase and topoisomerase IV (the quinolone resistance-determining regions) reduce drug binding. **Efflux pumps** and reduced porin entry lower the concentration inside the cell. Plasmid-borne genes, such as the *qnr* family, protect the target and can pass between bacteria, which allows low-level resistance to spread sideways. Several small steps together produce clinical failure.

Resistance to one fluoroquinolone usually means resistance to all of them. Exposure of gut bacteria to sub-lethal drug levels selects resistant E. coli and Campylobacter, which can reach people through food or direct contact.

For this reason the major regulators and WHO treat fluoroquinolones as **critically important** for human medicine. Responsible use means:

- Keep them for infections where culture and sensitivity, or clear clinical judgement, show that first-line drugs will not work.
- Never use them for routine prophylaxis, mass medication or growth promotion.
- Use the right dose for the full intended course. Under-dosing selects resistance.
- Avoid use in food animals unless the label allows it, and observe the withdrawal period. Rules on fluoroquinolone use in food-producing animals differ between countries and have changed over time. For India, check the current notification of the relevant authority and the label.

Nitroimidazoles

Metronidazole is the standard example, with others such as tinidazole, ronidazole and dimetridazole. These are **prodrugs**. In an anaerobic cell, low-redox-potential proteins donate electrons to the nitro group. The reduced form is a reactive radical that damages DNA and kills the organism. In aerobic cells, oxygen removes the electron again, so the drug stays inactive. That explains the **selective toxicity for anaerobes** and protozoa such as Giardia, Trichomonas and Entamoeba.

In dogs and cats metronidazole is used for anaerobic infections, giardiasis and some inflammatory bowel conditions. It penetrates tissues, bone and abscesses well and crosses the blood-brain barrier. Resistance is uncommon but increasing.

The main toxicity concern is **neurotoxicity**, usually seen with prolonged or excessive exposure, with signs such as ataxia, head tilt, nystagmus and seizures. Treatment is stopping the drug and supportive care. Nitroimidazoles are also considered potentially carcinogenic and mutagenic from laboratory evidence. For that reason they are prohibited in food-producing animals in many countries. Check the current Indian notification before any use in a food species.

Nitrofurans and common confusions

Nitrofurans include furazolidone, nitrofurazone and nitrofurantoin. Like nitroimidazoles they are reduced inside the bacterial cell to reactive intermediates that attack DNA and ribosomal proteins, so resistance develops slowly. They have a wide spectrum against Gram-positive and Gram-negative bacteria and some protozoa.

The important residue concept: nitrofuran parent drugs vanish quickly, but their **tissue-bound metabolites** persist for a long time and can be detected in meat, eggs and fish long after treatment. Because of concern about carcinogenicity of these residues, nitrofurans are banned in food animals in many countries, and testing programmes look for the metabolites. Whether and how they are permitted in India is a matter of current notification, so confirm before use. Nitrofurantoin remains a human urinary antiseptic, and in pets it is occasionally used for urinary infection because it concentrates in urine.

Common confusions to avoid:

- Fluoroquinolones act on DNA enzymes, but nitroimidazoles and nitrofurans damage DNA through reduction. Both end in DNA damage, but by different routes.
- Metronidazole is not effective against aerobes, and enrofloxacin is not reliable against anaerobes. Together they cover different gaps, but combination should be justified, not routine.
- A drug with good in vitro activity is not automatically safe in the species. Always check species and age limits.

Concept cleared

Trapped DNA breaks

Fluoroquinolones freeze gyrase and topoisomerase IV on cut DNA, so strand breaks cannot be repaired and the bacterium dies.

Concentration-dependent killing

The peak concentration relative to the MIC drives effect, so the aim is a high peak, not frequent small doses.

Prodrug activation in anaerobes

Nitroimidazoles become toxic only when reduced in low-oxygen cells, which gives anaerobe and protozoal selectivity.

Bound metabolite residues

Nitrofuran metabolites bind to tissue proteins and persist, so a short withdrawal period cannot be trusted and many countries ban the group in food animals.

Memory aid: Fluoroquinolone cautions: CART

Cartilage in young animals, Absorption blocked by cations, Retina in cats, Threshold for seizures lowered.

Compare and contrast

Fluoroquinolones vs nitroimidazoles vs nitrofurans

Feature	Fluoroquinolones	Nitroimidazoles	Nitrofurans
Main target	DNA gyrase and topoisomerase IV	DNA damage after reduction in anaerobes	DNA and protein damage after reduction
Spectrum	Aerobic Gram-negatives, Mycoplasma, some Gram-positives	Anaerobes and protozoa	Broad, includes some protozoa
Key concern	Cartilage damage, feline retinopathy, resistance	Neurotoxicity, carcinogenicity concern	Persistent residues, carcinogenicity concern
Food animal use	Restricted; check current rules	Prohibited in many countries; check Indian rules	Prohibited in many countries; check Indian rules

Enrofloxacin vs marbofloxacin

Feature	Enrofloxacin	Marbofloxacin
Active metabolite	Partly converted to ciprofloxacin	Not converted to ciprofloxacin
Feline retinal risk	Recognised at high exposure	Not a recognised concern at label use
Class concern	Critically important antibacterial	Critically important antibacterial
Interaction with cations	Chelation lowers absorption	Chelation lowers absorption

Species notes

Dogs

Avoid during the rapid growth period, especially in large breeds, because of cartilage damage. Metronidazole can cause neurological signs with prolonged exposure.

Cats

Enrofloxacin can cause retinal damage and blindness at excess exposure, so label limits matter. Marbofloxacin is often chosen when a quinolone is justified.

Poultry

Cattle and buffalo

Fluoroquinolone use in poultry is closely linked to resistant E. coli and Campylobacter reaching people, so rules are strict in many countries. Check the current notification for India.

Use in food animals depends on the label and local law. Withdrawal period for milk and meat must be observed and recorded.

Horses

Fluoroquinolones carry a risk of joint cartilage damage in foals, so they are generally avoided in young animals.

Clinical pearls

Self-test: 10 questions

1. The main target of fluoroquinolones in Gram-negative bacteria is:

Gyrase is the primary target in Gram-negatives, and topoisomerase IV in Gram-positives.

2. Which statement about fluoroquinolone killing is correct?

The peak concentration relative to MIC drives the bactericidal effect.

3. A classic toxicity of enrofloxacin in cats is:

Retinal toxicity and blindness are linked to high exposure in cats.

4. Why are fluoroquinolones avoided in growing puppies of large breeds?

Joint cartilage erosion is seen in growing animals.

5. Which co-administered product reduces fluoroquinolone absorption?

Divalent and trivalent cations chelate the drug in the gut.

6. Which fluoroquinolone is partly converted to ciprofloxacin?

Enrofloxacin is partly de-ethylated to ciprofloxacin; marbofloxacin is not.

7. Metronidazole is selectively toxic to anaerobes because:

Oxygen reverses the activation, so aerobes are spared.

8. A sign of metronidazole neurotoxicity in dogs is:

Central vestibular signs follow prolonged or excessive exposure.

9. Why do nitrofurans cause special residue concern?

Bound metabolites can be found in tissues long after the parent drug has gone.

10. Which practice is NOT responsible fluoroquinolone use?

Routine prophylaxis with critically important drugs selects resistance.

Key points to revise

1. Fluoroquinolones inhibit DNA gyrase and topoisomerase IV and are bactericidal.
2. They have poor activity against anaerobes.
3. Cartilage damage in young animals and retinal damage in cats are the classic toxicities.

4. Cations chelate fluoroquinolones and reduce absorption.
5. Resistance arises by target mutations, efflux and plasmid-borne protection genes.
6. Nitroimidazoles are prodrugs activated in anaerobes and are neurotoxic when overexposed.
7. Nitrofurans leave persistent tissue-bound residues, and many countries ban them in food animals.
8. Responsible use means reserving critically important drugs for proven need and following local rules, which for India must be checked in the current notification.

Go deeper on this site

- Ch 8. Polypeptide and miscellaneous antibiotics (in this book)
- Ch 6. Macrolides, lincosamides and pleuromutilins (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Wikipedia: Fluoroquinolone
- Wikipedia: Nitroimidazole
- FDA Center for Veterinary Medicine: Antimicrobial resistance

CHAPTER 8 OF 19

Polypeptide and miscellaneous antibiotics

Polymyxins (colistin), bacitracin, glycopeptides such as vancomycin and the ionophore antibiotics each work by an unusual mechanism and each carries a distinct stewardship message. The chapter covers why colistin is protected as a last-resort drug and why ionophores are dangerous to non-target species.

After this chapter you can

- Explain how polymyxins disrupt the Gram-negative outer membrane and why they are nephrotoxic
- Describe the status of colistin in food animals and the problem of plasmid-borne resistance, with hedged Indian rules

- Explain the mechanism and use of bacitracin and why it is applied topically
- Describe how vancomycin works and how vancomycin resistance arises
- Explain how ionophores act, their uses in poultry and ruminants, and why they are toxic to horses and dogs

Why these drugs are grouped together

The drugs in this chapter do not belong to one family. They are grouped because each is either a peptide in structure or acts by an unusual mechanism, and because most are poorly absorbed or too toxic for general systemic use. Their value lies in narrow roles: topical use, gut-restricted use, last-resort treatment of resistant Gram-negative infection, or coccidiosis control.

Ask three questions for each drug. What does it attack? Why is it not used like penicillin? What is the stewardship message? The answers follow from the mechanism.

Polymyxins and colistin

Polymyxin B and polymyxin E (**colistin**) are cationic peptides with a fatty tail. The outer membrane of Gram-negative bacteria carries negatively charged lipopolysaccharide (LPS). The positively charged polymyxin binds LPS, displaces the calcium and magnesium that stabilise it, and disrupts the membrane. The cell leaks and dies. The effect is **bactericidal** and does not need the cell to be dividing.

Because the target is the Gram-negative outer membrane, the spectrum is limited to **Gram-negative bacteria** including Pseudomonas, Klebsiella, E. coli and Acinetobacter. Gram-positive bacteria, anaerobes and some naturally resistant genera such as Proteus are not covered.

Absorption from the gut is negligible. This has two consequences. Oral colistin acts in the gut lumen, which made it popular for enteric colibacillosis in young animals. By injection, however, the drug causes **nephrotoxicity and neurotoxicity**, so systemic use is limited to serious infections where other drugs have failed. Polymyxins can also cause neuromuscular blockade, which is worsened by anaesthetics or muscle relaxants.

Colistin is now valued in human medicine as a **last-resort drug** against carbapenem-resistant Gram-negative infection. A plasmid gene, *mcr-1*, was found in bacteria from animals and people, and it moves between bacteria and species. Because heavy use in livestock was seen as driving this resistance, many countries restricted colistin in food animals. India has taken a regulatory step to prohibit colistin in food-producing animals, including as a growth promoter, but you should check the current notification for exact scope, dates and exceptions.

Bacitracin

Bacitracin is a polypeptide produced by *Bacillus subtilis*. It blocks the recycling of a lipid carrier that moves cell wall building blocks across the membrane. Without the carrier, peptidoglycan cannot be completed. The target is a different step from penicillin, so there is no cross-resistance with beta-lactams.

Spectrum is mainly Gram-positive cocci and rods. Bacitracin is **too nephrotoxic for systemic use**, so it is used topically, often in ointments combined with neomycin and polymyxin to widen the spectrum, in eye and skin preparations.

Zinc bacitracin and similar salts have been used in feed as growth promoters because they are poorly absorbed and act in the gut. Growth promotion with antibiotics is increasingly restricted worldwide for stewardship reasons. For India, check the current notification and label for any permitted feed use.

Vancomycin and the glycopeptides

Vancomycin is a large glycopeptide. It binds the **D-alanyl-D-alanine** end of the peptidoglycan precursor and physically blocks the transpeptidase and transglycosylase enzymes from using it. The mechanism is different from beta-lactams, which bind the enzyme itself.

It is active against Gram-positive bacteria including methicillin-resistant staphylococci and Clostridioides difficile, but it cannot cross the Gram-negative outer membrane, so Gram-negatives are not covered. It is not absorbed orally, so it is given intravenously for systemic infection and orally only for gut infections. Adverse effects include nephrotoxicity and ototoxicity, and rapid infusion can cause histamine-mediated flushing.

Resistance in enterococci arises when the terminal D-Ala-D-Ala is replaced by **D-Ala-D-lactate**, which vancomycin binds poorly. The genes (van genes) can spread between bacteria. A famous lesson: avoparcin, a related glycopeptide once used as a growth promoter, was linked to vancomycin-resistant enterococci in farm animals, and it was withdrawn in several regions. Vancomycin itself is not a routine veterinary drug and is held in reserve for resistant infections in companion animals where culture supports its use.

Stewardship lessons and common confusions

Each drug in this chapter teaches a stewardship point. Colistin shows how a drug used for convenience in animals can threaten a human last-resort option, because the resistance gene sits on a plasmid and crosses species. Vancomycin and avoparcin show how a related drug used in feed can select resistance to the human drug. Bacitracin shows how a drug can be useful precisely because it stays on the surface or in the gut. Ionophores show that a drug with no human use can still be dangerous in the wrong animal.

Common confusions:

- **Poor absorption does not mean no resistance.** Gut-restricted drugs still expose the huge bacterial population of the intestine and can select resistant bacteria.
- **Bacitracin and vancomycin both affect cell wall synthesis** but at different steps, and neither is a beta-lactam. There is no cross-resistance with penicillins.
- **Ionophores are called antibiotics but are used mainly as coccidiostats and production aids.** Their rules and their toxicity profile differ from antibiotics used for treatment.
- **Polymyxin B and colistin** are closely related and cross-resistant, so resistance to one predicts resistance to the other.

In practice, record every medicated feed, check the species on the label, and treat any ban or restriction notified by the Indian authorities as binding. Look up the current notification for the exact scope.

Ionophore antibiotics

Monensin, salinomycin, lasalocid and narasin are produced by *Streptomyces*. They are lipid-soluble molecules that bind positive ions (sodium, potassium, calcium) and

carry them across membranes, destroying the ion gradients that cells need. Organisms with high ion demands, such as Gram-positive bacteria and coccidial protozoa, are affected. Gram-negatives are protected by the outer membrane.

Uses in veterinary medicine:

- **Poultry:** coccidiostats in feed. Resistance develops slowly, since the mechanism is physical and not a single enzyme target.
- **Ruminants:** improve feed efficiency. They shift rumen fermentation toward propionate, reduce lactic acid and methane production, and help prevent coccidiosis and bloat in some systems.

Ionophores are not used in human medicine, so concern about cross-resistance to human drugs is smaller than for other classes. The real concern is **toxicity**. Horses are extremely sensitive and develop cardiac and skeletal muscle damage from contaminated feed. Dogs, cats and some birds such as turkeys can also be poisoned. Cattle are tolerant at label levels but are poisoned by feed-mixing errors. Signs include anorexia, weakness, dyspnoea and sudden death. Mixing errors and wrong species feeding are the commonest causes.

Ionophores also interact with drugs such as tiamulin, which can raise toxicity because tiamulin slows their metabolism. Never mix them in feed meant for horses, and always keep records of which feed went to which flock or herd.

Concept cleared

Membrane attack on Gram-negatives
Cationic polymyxins bind LPS and break the outer membrane, so they act only on Gram-negative bacteria and are toxic to kidney and nerve.

Poor absorption decides the use
Bacitracin and oral colistin and vancomycin stay in the gut or on the skin, which is both their purpose and the reason systemic toxicity limits injection.

Binding the substrate, not the enzyme

Vancomycin binds D-Ala-D-Ala so cell wall enzymes cannot use it, and resistance swaps the terminal to D-Ala-D-lactate.

Ionophore selectivity and danger

Ionophores wreck ion gradients, helping against Gram-positives and coccidia, but the same action poisons horses and dogs.

Memory aid: Four P-B-V-I roles

Polymyxin breaks the outer membrane, Bacitracin blocks the carrier, Vancomycin binds the D-Ala tail, Ionophores wreck the ion gradient.

Compare and contrast

Polypeptide and glycopeptide antibiotics

Drug	Target	Spectrum	Main limitation
Colistin / polymyxin B	LPS and outer membrane	Gram-negative	Nephrotoxic, neurotoxic, last-resort status
Bacitracin	Lipid carrier in cell wall synthesis	Gram-positive	Nephrotoxic, topical use only
Vancomycin	D-Ala-D-Ala of peptidoglycan precursor	Gram-positive	Not absorbed orally, resistance via D-Ala-D-Lac
Ionophores	Ion gradients across membranes	Gram-positive and coccidia	Toxic to horses, dogs and turkeys

Oral colistin vs injectable colistin

Feature	Oral	Injectable
Absorption	Negligible	Complete by route
Site of action	Gut lumen	Systemic
Toxicity	Low	Kidney and nerve toxicity
Stewardship	Food animal use restricted in many countries; check Indian notification	Reserve for resistant infection under veterinary control

Species notes

Poultry

Ionophores are used as coccidiostats. Never feed these medicated feeds to other species and observe withdrawal periods. Colistin use as a feed additive is a stewardship concern, so check current Indian rules.

Horses

Extremely sensitive to ionophores. Accidental feeding of poultry or cattle feed has caused fatal cardiac and muscle damage.

Dogs and cats

Susceptible to ionophore poisoning from poultry feed or cattle feed. Topical bacitracin combinations are used for skin and eye problems.

Cattle and buffalo

Ionophores improve rumen efficiency at label levels, but mixing errors cause toxicity. Colistin was used for enteric disease in calves but is restricted in food animals in many places.

Pigs

Oral polymyxins have been used for post-weaning E. coli diarrhoea, which is the type of use now under scrutiny because of mcr resistance.

Clinical pearls

Self-test: 10 questions

1. Polymyxins act by:

Their cationic structure binds LPS and breaks the Gram-negative outer membrane.

2. Which organisms are covered by colistin?

The target is found only on Gram-negative cells.

3. The main toxicity of injected colistin is:

Kidney and nerve toxicity limits systemic use.

4. The plasmid gene linked with transferable colistin resistance is:

mcr-1 modifies LPS and spreads between bacteria.

5. Why is bacitracin used topically?

It is nephrotoxic when absorbed, so topical use is safer.

6. Vancomycin binds to:

This blocks cell wall enzymes from using the substrate.

7. Vancomycin resistance in enterococci involves:

The altered terminus binds vancomycin poorly.

8. Ionophores act by:

They collapse ion gradients in susceptible cells.

9. Which species is most sensitive to ionophore poisoning?

Horses develop cardiac and skeletal muscle damage from small exposure.

10. Ionophores are not effective against Gram-negative bacteria because:

The outer membrane blocks entry of these molecules.

Key points to revise

1. Polymyxins bind LPS and disrupt the outer membrane of Gram-negative bacteria.
2. Injected polymyxins are nephrotoxic and neurotoxic.
3. Plasmid-borne mcr resistance threatens colistin as a last-resort drug.
4. Check the current Indian notification for colistin and feed additive rules.
5. Bacitracin inhibits cell wall synthesis and is used topically.
6. Vancomycin binds D-Ala-D-Ala and is active against Gram-positives only.
7. Ionophores carry ions across membranes and are used as coccidiostats and rumen modifiers.
8. Ionophores are highly toxic to horses and also to dogs and turkeys.

Go deeper on this site

- Ch 9. Antimicrobial resistance and stewardship (in this book)
- Ch 7. Fluoroquinolones and other synthetic antibacterials (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Wikipedia: Polymyxin
- Wikipedia: Ionophore
- FDA Center for Veterinary Medicine: Antimicrobial resistance

CHAPTER 9 OF 19

Antimicrobial resistance and stewardship

How bacteria become resistant, how resistance spreads between animals, people and the environment, and what a veterinarian does about it. Covers the WHO AWaRe idea, withdrawal periods and residue limits, and why treatment records matter.

After this chapter you can

- Describe the main biochemical mechanisms of antimicrobial resistance
- Explain how resistance genes spread between bacteria and between species
- Explain the AWaRe classification idea and how it guides drug choice
- Explain withdrawal period, MRL and why FSSAI limits (hedged) matter for food safety
- List the elements of good stewardship and treatment record keeping

What resistance means

A bacterium is **resistant** when it can grow at drug concentrations that would normally stop it. In the laboratory this is measured by the **minimum inhibitory concentration (MIC)** and compared with a breakpoint set by expert committees. Treatment fails when the concentration that can safely be reached in the patient is not high enough relative to the MIC.

Resistance can be **intrinsic**, a natural feature of the species (for example, Gram-negatives are naturally protected from vancomycin by the outer membrane), or **acquired**, through mutation or gene transfer. Antimicrobial resistance is recognised by WHO as a major global health threat. Use in animals, in people and in the environment all contribute, which is the **One Health** view.

An important idea: antimicrobials do not create resistance genes in most cases. They **select** bacteria that already carry them. Every exposure, particularly to low or inadequate concentrations, gives the resistant survivors room to multiply.

Mechanisms of resistance

Bacteria use a small number of strategies, and each links to a drug class you already know.

- **Enzymatic inactivation.** Beta-lactamases break the beta-lactam ring. Other enzymes modify aminoglycosides or chloramphenicol.
- **Target change.** The binding site is altered so the drug no longer fits. Examples: altered penicillin-binding protein in MRSA, gyrase mutation for fluoroquinolones, ribosomal methylation for macrolides, D-Ala-D-Lac for vancomycin.
- **Reduced entry.** Loss or narrowing of porins in Gram-negative outer membranes.
- **Efflux.** Pumps remove the drug as fast as it enters, which is common with tetracyclines and fluoroquinolones.
- **Bypass.** The cell uses another pathway or makes extra target, as with resistance to trimethoprim or sulphonamides.

Other protective states are not genetic. **Biofilms** embed bacteria in a matrix where drug penetration is poor and cells grow slowly, and **persister** cells survive without being genetically resistant. This is why infections on implants, in the udder or in chronic wounds often relapse.

How resistance spreads

Resistance spreads by **vertical** inheritance when a resistant cell divides, and by **horizontal gene transfer** between cells. The three routes are conjugation (direct transfer of plasmids through contact), transduction (carried by bacteriophage) and transformation (uptake of free DNA).

Plasmids can carry several resistance genes at once. This gives **co-selection**: using one drug selects bacteria that are also resistant to other drugs on the same plasmid. A farm using tetracycline may thereby maintain resistance to other classes as well.

Resistant bacteria travel on food, water, manure, hands, hospital surfaces and wildlife. A dog with a resistant skin infection can share the organism with its owner. A resistant E. coli from poultry can colonise people who handle the birds. Residues of antibiotics in manure and water can keep selecting resistance in the environment.

Stewardship and the AWaRe idea

Stewardship means using antimicrobials so that they cure the patient and stay effective for the future. The WHO **AWaRe** framework sorts antibiotics into three groups for human medicine:

- **Access:** first- and second-choice drugs with narrower spectrum and lower resistance potential, which should be widely available.
- **Watch:** drugs with higher resistance potential, whose use should be limited to specific indications and monitored.
- **Reserve:** last-resort drugs for multi-resistant infections, used with strict oversight.

Veterinary medicine borrows the same logic: start with narrow, first-line drugs, restrict the critically important ones such as fluoroquinolones, third-generation cephalosporins and colistin, and keep last-resort drugs for people. The exact lists for animals differ, so use the current WOAH or national list.

Practical stewardship steps:

1. Confirm that the condition is bacterial and needs treatment. Viral and many self-limiting conditions do not.
2. Take samples for culture and sensitivity before treatment where possible, especially in recurrent or serious cases.
3. Choose the narrowest effective drug and a route that reaches the site.
4. Use the correct dose and duration, and avoid sub-therapeutic exposure.
5. Do not use antibiotics for growth promotion or routine prophylaxis.
6. Prevent disease through vaccination, hygiene, nutrition and biosecurity.
7. Review the response and stop when appropriate.

Withdrawal periods, residue limits and food safety

When a drug is given to a food-producing animal, residues can remain in milk, meat, eggs and honey. The **withdrawal period** is the minimum time that must pass between the last dose and the collection of milk or slaughter of the animal so that residue levels have fallen below the legal limit. It depends on the drug, formulation, route, species and product. The label of the product is the authority, and the period

may be longer if the animal has liver or kidney disease or if the product is used outside the label.

The legal limit is the **maximum residue limit (MRL)**: the highest residue concentration of a substance accepted in a food. In India the Food Safety and Standards Authority (FSSAI) regulates antibiotic and pharmacologically active substance limits in food. Limits, listed substances and the regulations are amended from time to time, so check the current FSSAI notification and the label.

Why residues matter: they can cause allergy in sensitive consumers, disturb human gut bacteria, select resistant bacteria and, in milk, interfere with fermentation in dairy products. Milk from treated animals during withdrawal must be discarded, not mixed in the bulk tank. Using a drug extra-label, for example a drug prohibited in food animals, can make residues illegal regardless of the interval.

Records are the tool that makes all this work. A **treatment record** should note the animal identity, date, diagnosis, drug and batch, dose, route and duration, the person treating, and the earliest date for milk or slaughter. Good records let you trace a residue violation, check compliance, review which drugs are used most, and justify decisions. Keep culture reports and prescriptions with them.

Surveillance, One Health and the veterinarian's role

Resistance cannot be managed by one clinic alone. **Surveillance** programmes collect resistance data from animals, food, people and the environment so that trends can be seen and policy can be set. Veterinary laboratories contribute by reporting culture and sensitivity results accurately and by following standard methods and breakpoints.

The veterinarian has several roles. As a prescriber, you decide whether an antimicrobial is needed, which one and for how long. As an adviser, you explain to farmers why completing a course matters, why leftover tablets must not be shared or reused, and why a milk discard period is not optional. As a record keeper, you provide the data that makes surveillance and food safety checks possible.

Common confusions:

- **A resistant bacterium does not make the animal resistant.** The resistance belongs to the microbe, not the patient.

- **Stopping a course early is not the main cause of resistance.** The bigger drivers are unnecessary use and exposure to inadequate drug levels. Duration should be as short as is effective.
- **Rotating drugs does not by itself fix resistance.** Reducing total use and choosing correctly does more.
- **A sensitive result in the laboratory does not guarantee cure.** Site of infection, drug penetration and host defence still matter.

Farmers should be advised to follow only the veterinarian's prescription, to avoid buying antibiotics over the counter for self-medication, and to keep the treatment record on the farm.

Concept cleared

Selection, not creation
Antimicrobials usually select resistant bacteria already present, so every unnecessary or under-dosed course increases the resistant share.

Five resistance mechanisms
Inactivating enzymes, altered targets, reduced entry, efflux and bypass explain nearly all acquired drug resistance.

Horizontal transfer and co-selection
Plasmids move between bacteria and often carry several genes, so one drug can maintain resistance to many.

Withdrawal period and MRL
The withdrawal period is the time needed for residues to fall below the MRL, and recorded treatment dates make it enforceable.

Memory aid: Resistance mechanisms: DREAM
Destroy the drug, Reduce entry, Efflux it, Alter the target, bypass by Making another pathway.

Compare and contrast

AWaRe groups

Group	Idea	Veterinary translation
Access	First-line, narrow spectrum	Preferred starting choices
Watch	Higher resistance potential, limited indications	Use after sensitivity evidence; restrict critically important drugs
Reserve	Last resort for multi-resistant infections	Keep for people; avoid in food animals

Intrinsic vs acquired resistance

Feature	Intrinsic	Acquired
Origin	Natural trait of the species	Mutation or gene transfer
Predictability	Predictable from species	Needs testing
Example	Gram-negatives and vancomycin	ESBL-producing E. coli
Spread	Not transferable	Can spread horizontally

Species notes

Dairy cattle and buffalo
Milk withdrawal must be observed and recorded. Mastitis treatment should follow culture where possible, and dry-cow therapy should not be routine for every quarter.

Poultry
Flock-level treatment and prophylaxis drive resistance in E. coli and Salmonella. Biosecurity and vaccination are preferred. Eggs and meat have separate withdrawal rules.

Pigs
In-feed medication for groups raises co-selection risk. Follow label and avoid routine prophylaxis.

Dogs and cats
Resistant skin and urinary pathogens such as MRSP and ESBL E. coli can be shared with owners. Culture

before using critically important drugs.

Horses
Hospital-acquired resistant infections occur, so hygiene and surgical prophylaxis protocols matter. Check rules on equine use in the food chain.

Clinical pearls

Self-test: 10 questions

1. Resistance by beta-lactamase is an example of:

The enzyme breaks the beta-lactam ring.

2. Which mechanism is typical of tetracycline resistance?

Efflux pumps are a common mechanism for tetracyclines.

3. Transfer of plasmid DNA through direct cell contact is:

Conjugation uses direct contact.

4. Transfer of DNA by bacteriophage is called:

Phages carry bacterial DNA between cells.

5. In AWaRe, Reserve antibiotics are:

They are kept for infections that no other drug can treat.

6. The withdrawal period is:

It lets residues fall below the MRL.

7. MRL stands for:

It is the highest accepted residue concentration in food.

8. Co-selection occurs when:

Selecting for one gene retains the others on the same element.

9. Which is NOT a stewardship step?

Routine prophylaxis selects resistance and is discouraged.

10. Relapse of udder or implant infection despite a susceptible organism may be explained by:

Biofilms limit drug penetration and protect slow-growing cells.

Key points to revise

1. Resistance is measured by MIC against a breakpoint.
2. Mechanisms: enzyme inactivation, target change, reduced entry, efflux and bypass.
3. Horizontal transfer occurs by conjugation, transduction and transformation.
4. Resistance in animals, people and the environment is linked through One Health.
5. AWaRe groups antibiotics as Access, Watch and Reserve.
6. Withdrawal period is the time for residues to fall below the MRL.
7. FSSAI regulates antibiotic residue limits in India, so check the current notification.

8. Treatment records, culture reports and narrow-spectrum first-line choices are the base of stewardship.

Go deeper on this site

- Ch 10. Drug residues, MRLs and food safety (in this book)
- Ch 8. Polypeptide and miscellaneous antibiotics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Concepts
- Veterinary Drug Concepts Clearly Explained

Sources

- WHO: Antimicrobial resistance fact sheet
- FDA Center for Veterinary Medicine: Antimicrobial resistance
- Wikipedia: Antimicrobial resistance

CHAPTER 10 OF 19

Drug residues, MRLs and food safety

Why traces of veterinary drugs persist in milk, meat, eggs and honey, how maximum residue limits and withdrawal periods protect the consumer, and how the Indian food-safety system, testing and farm practice fit together. Written for the veterinarian who prescribes the drug and therefore owns the residue risk.

After this chapter you can

- Explain why residues occur and which animal products are affected
- Define ADI, MRL and withdrawal period and describe how they relate to each other
- Explain why withdrawal periods differ between milk, meat, eggs and honey
- Outline the Indian food-safety framework for residues, with appropriate hedging
- Describe screening and confirmatory testing and the farm practices that prevent violations

What a residue is and why it matters

A **drug residue** is the parent drug, its metabolites, or related substances that remain in an edible product after treatment. The animal's body does not clear a drug at the moment treatment stops. Elimination follows the pharmacokinetics you studied earlier, so some drug stays in blood and tissues for a time, and a part of it enters milk, eggs or honey.

Residues matter for several reasons. Some people are sensitised to drugs such as penicillins, and a trace in milk can trigger a reaction. Sub-inhibitory antibiotic exposure through food may favour resistant gut bacteria. Some drugs are toxic or carcinogenic to humans and have no place in food animals at all. Finally, antibiotic in milk has a technological cost: it inhibits the starter cultures used for curd, yoghurt and cheese, so processors reject such milk.

Residue control is a food-safety duty shared by the farmer, the veterinarian, the processor and the regulator. The veterinarian is the key person because the treatment decision, and the advice on withholding the product, starts with the prescription.

Residues in milk, meat, eggs and honey

Each product behaves differently, and this is why one drug can carry several different withdrawal times.

- **Milk.** Many drugs reach milk by passive diffusion. Weak bases are trapped in milk because milk is slightly more acidic than plasma (ion trapping), and lipid-soluble drugs concentrate in milk fat. Intramammary products leave high local concentrations in the udder. Milk is consumed fresh and pooled, so one treated cow can contaminate a whole tank.
- **Meat and offal.** Residues persist in tissues. Kidney and liver often hold the highest levels because they handle elimination, and injection sites can keep drug for a long time. Tissue binding and depot formulations lengthen the stay.
- **Eggs.** Drug may be deposited in yolk or albumen during egg formation, and the effect lasts until the follicles that formed during treatment have been laid. Many drugs are not approved for layers whose eggs are for human consumption.
- **Honey.** Bees are food-producing animals too. Antibiotics put in hives for brood disease can remain in honey for a long period because honey does not

metabolise them. Honey is therefore a well-known problem product in international trade.

Remember that residues are not only antibiotics. Anthelmintics, anti-inflammatories such as NSAIDs, hormones, coccidiostats and pesticides used as ectoparasiticides can all appear.

ADI, MRL and the logic of the safe limit

Regulators work backwards from human safety, in steps.

1. Toxicology studies identify a level with no observed adverse effect. A safety factor is applied to give the **acceptable daily intake (ADI)**, the amount a person can consume every day for life without appreciable risk.
2. Using typical food consumption, the ADI is divided among the foods that may contain the drug. This gives the **maximum residue limit (MRL)**, the highest concentration of residue legally accepted in a specified food (for example muscle, liver, kidney, milk, eggs).
3. Studies of how fast residues fall in the target tissue show when the residue has dropped below the MRL. That time, with an added margin, becomes the **withdrawal period** (also called withholding period).

At international level, expert committees such as JECFA evaluate veterinary drugs and the Codex Alimentarius Commission adopts MRLs that countries can use as a reference. Individual countries and trading blocs may set their own values, so an MRL for a drug in one market can differ from another. For India, always check the current notification of the food regulator for the value that applies.

A common confusion: an MRL is a legal and analytical limit, not a toxic threshold. A level just above it is not automatically harmful, but it is a violation. The ADI is the health-based figure and the MRL is the enforcement figure derived from it.

Withdrawal-period logic

The withdrawal period is the minimum time between the last dose and the collection of milk, eggs, honey or slaughter for meat. It applies to a product, a species, a formulation and a route, because each of these changes the elimination curve. A withdrawal period set for an injectable in one species cannot be copied to another species or to a long-acting form.

Factors that lengthen real residue persistence include:

- Liver or kidney disease, which slows metabolism and excretion.
- Depot or long-acting formulations and large intramuscular volumes at one site.
- Higher doses or longer courses than the label, and repeated treatments.
- Poor feed intake, dehydration and heavy milk yield changes in mastitis.
- Combining drugs that compete for elimination.

Extra-label use is the key trap. When a drug is used outside its label, the labelled withdrawal no longer protects anyone, because it was never measured for that use. The veterinarian must then take responsibility for a conservative, justified withdrawal, ideally supported by published data or by advice from a residue authority. If no reliable figure exists, the safe choice is not to use the drug in food animals.

Also note that milk and meat withdrawals are different numbers for the same drug, and the longer one applies to a cull animal whose milk has already been discarded. Treating a cow does not stop at the end of the milk discard time if she is going to the abattoir.

The Indian food-safety system

In India, food safety is governed by the Food Safety and Standards Act, 2006, under which the Food Safety and Standards Authority of India (FSSAI) frames standards and regulations for food, including contaminants and residues. Veterinary drug and antibiotic limits in foods of animal origin are set through FSSAI regulations and amendments, and some uses of antimicrobials in food animals have been restricted or banned by the drug and veterinary authorities. These rules change from time to time. Students should **check the current notification** for any particular drug, limit or ban rather than relying on a textbook list.

Other parts of the system also matter. State animal husbandry and dairy departments, dairy cooperatives and large processors run milk-quality programmes, and export-oriented products such as shrimp, meat and honey are tested for residues under separate export-residue monitoring arrangements to meet importing-country limits. Antimicrobial stewardship policies, such as national action plans against resistance, link residue control to the wider resistance problem.

In practice, the weak points are often not the law but its enforcement: unrecorded treatment, sale of milk during treatment, over-the-counter drug supply and the use of banned or human-use drugs. The veterinarian can help by prescribing only appropriate products, keeping treatment records, and explaining the withdrawal in language the farmer will follow.

Testing and compliance on farms

Residue testing uses two tiers. **Screening tests** are quick and cheap and are meant to catch most positives. They include microbial inhibition tests, in which antibiotic stops bacterial growth or a colour change, and receptor-binding or lateral-flow strip tests, often designed for beta-lactams and tetracyclines. They tell you that an inhibitory substance may be present but usually not which one, and false positives and false negatives are possible. **Confirmatory tests**, mostly chromatography with mass spectrometry, identify the compound and measure its concentration against the MRL, and are used for legal action.

Compliance on the farm rests on simple habits:

- Identify every treated animal clearly and record drug, date, route and the date the product can be used.
- Keep treated animals' milk separate and discard it for the full period, including milk from all quarters, not only the treated one.
- Use the label dose and route, and avoid unneeded extra-label use.
- Keep feed and water free of medicated material meant for other animals, since carry-over also causes residues.
- Do not send treated animals to slaughter before the meat withdrawal has passed.
- Prevent discarded milk being fed to calves without thought, since this exposes them to antibiotic.

Good practice also protects the farmer: milk rejected at the dairy plant is a direct financial loss, and repeated violations can end supply contracts.

Concept cleared

ADI and MRL are different

ADI is a health-based intake figure derived from toxicology. MRL is an enforcement limit in a particular food, derived from the ADI and food consumption. The withdrawal period is the time needed for residue to fall below the MRL.

Withdrawal is product-specific

A drug can have different withdrawal times for milk, meat, eggs and honey, and for different species, doses, routes and formulations. A single number cannot be borrowed across these.

Extra-label use removes the safety margin

Labelled withdrawal was measured only for the labelled use. Outside the label the veterinarian must justify a conservative period or avoid the drug in food animals.

Residues carry three risks

They can cause hypersensitivity, favour resistance, and disrupt dairy processing. Some substances are banned in food animals regardless of any limit.

Memory aid: ADI then MRL then WP

A Dose Is safe (ADI), More Residue Lost (MRL) gives the legal limit, Wait Patiently (WP) until residue falls below it. Order: safe intake, legal limit, waiting time.

Compare and contrast

Residue behaviour by product

Product	Main route into product	Why it persists	Practical point
Milk	Diffusion from blood; direct from intramammary route	Ion trapping and fat solubility; udder depot	Pooled milk; discard milk from all quarters
Meat and offal	Tissue distribution and binding	Liver, kidney and injection-site depots	Meat withdrawal applies even after milk discard ends
Eggs	Deposition during yolk and albumen formation	Drug present until treated follicles are laid	Many drugs not approved for table-egg layers
Honey	Direct addition to hives	Not metabolised in honey	Major trade problem; avoid antibiotics in honey flow

ADI, MRL and withdrawal period

Term	Meaning	Set by	Used for
ADI	Daily lifetime intake without appreciable risk	Toxicology and a safety factor	Starting point for the MRL
MRL	Maximum legal residue concentration in a food	Regulators, with Codex or national bodies as reference	Enforcement and trade
Withdrawal period	Time from last dose to collection or slaughter	Residue-depletion studies on the product	Farm and veterinary decisions
Extra-label withdrawal	Veterinarian's justified conservative period	Prescribing veterinarian	Use outside the label

Species notes

Dairy cattle and buffalo

Milk and meat withdrawals are separate. Milk from every quarter is discarded after systemic or intramammary treatment. Pooling in village collection makes a single

Sheep and goats

Few products are licensed for these species, so extra-label use is common and withdrawal times must be chosen with care. Goat milk is often used for human consumption.

treated animal a risk to many suppliers.

Poultry
Eggs and meat have separate considerations. Medication through drinking water or feed reaches the whole flock, so withdrawal must cover every bird and line. Many antimicrobials are not suitable for laying hens.

Pigs
In-feed medication is common, so carry-over in feed mills and shared feeders can produce residues. Observe the full meat withdrawal before slaughter.

Honey bees
Antibiotics for brood disease can persist in honey. Treat only outside honey flow and prefer management and hygiene over drug use.

Clinical pearls

Self-test: 10 questions

1. The maximum residue limit (MRL) is best defined as:

MRL is an enforcement limit for a particular food. The time is the withdrawal period, and the toxicity figure is not what an MRL represents.

2. The acceptable daily intake (ADI) is derived mainly from:

ADI is a health-based figure from toxicology, which regulators then use to set MRLs.

3. Why can ion trapping increase drug concentration in milk?

Weak bases ionise in the slightly acidic milk and cannot easily diffuse back to plasma.

4. A drug is used outside its label in a dairy cow. The labelled withdrawal:

Labelled withdrawals were generated only for the labelled use.

5. Which statement about honey is correct?

Honey does not metabolise antibiotics, so residues can persist and affect trade.

6. A rapid strip test in milk is positive for beta-lactam. This should be interpreted as:

Screening tests are presumptive. Confirmation with chromatography and mass spectrometry is the legal standard.

7. Which factor is most likely to lengthen actual residue persistence?

Depots release drug slowly and keep tissue levels above the limit for longer.

8. A cow treated for mastitis has finished her milk discard time but is sold for slaughter. What must be checked?

Milk and meat withdrawals are separate and the tissue withdrawal may be longer.

9. The international body that adopts reference MRLs for veterinary drugs in food is:

Codex adopts MRLs after expert evaluation, for example by JECFA, as international reference values.

10. Which statement about Indian rules on veterinary drug limits is most appropriate?

Limits and bans are revised over time, so the current notification is the authority.

Key points to revise

1. A residue is the drug or its metabolites remaining in food after treatment.
2. Residues can cause allergy, favour resistance and spoil dairy fermentation.
3. ADI is health-based; MRL is the enforcement limit for a food.
4. Withdrawal period is the time needed for residue to fall below the MRL.
5. Milk, meat, eggs and honey each need their own withdrawal consideration.
6. Extra-label use removes the protection of the labelled withdrawal.
7. Indian limits and bans are set through FSSAI and other authorities; check the current notification.
8. Good records, animal identification and separation of treated milk prevent most violations.

Go deeper on this site

- Ch 11. Mastitis and intramammary therapy (in this book)
- Ch 9. Antimicrobial resistance and stewardship (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Concepts
- Veterinary Drug Concepts Clearly Explained

Sources

- Codex Alimentarius, FAO and WHO
- Food Safety and Standards Authority of India
- WHO, Antimicrobial resistance fact sheet

CHAPTER 11 OF 19

Mastitis and intramammary therapy

How the udder environment and the causal organism decide whether antibiotic therapy will work, and how lactating-cow therapy, dry-cow therapy, teat sealants and dips are used. The chapter links treatment choice to culture, residue control and the reduction of antibiotic use on dairy farms.

After this chapter you can

- Explain why pathogen type and udder physiology determine treatment success
- Distinguish contagious from environmental mastitis and the therapeutic consequence of each
- Compare lactating-cow and dry-cow therapy, including blanket and selective approaches
- Describe how teat sealants and teat dips prevent new infection
- Outline residue management and strategies to reduce antibiotic use in mastitis control

Why mastitis therapy is different

Mastitis is inflammation of the mammary gland, usually caused by bacteria that enter through the teat canal. It is the commonest reason for antimicrobial use in dairy herds, and it is also the commonest cause of antibiotic residues in milk. Therapy is not as simple as choosing a drug that kills the organism in a test tube.

Three features of the udder complicate treatment. First, the alveoli and ducts are a closed tree, so drug placed in the teat may not reach infected deep tissue, especially when ducts are blocked by swelling and debris. Second, milk is a poor environment for many drugs: its pH, fat and protein content change activity. Third, some bacteria live inside host cells or in microabscesses, where drug concentrations are low.

For this reason, treatment decisions should consider the organism, the stage of lactation, the duration of infection and the likelihood of cure, not only the clinical signs.

Contagious and environmental pathogens

The grouping of pathogens guides both therapy and control.

- **Contagious pathogens** spread from cow to cow, mainly at milking. Examples are *Streptococcus agalactiae*, *Staphylococcus aureus* and *Mycoplasma* species. Control relies on milking hygiene, post-milking teat dips, milking order and culling of chronic carriers.
- **Environmental pathogens** come from bedding, manure and wet surroundings. Examples are *Escherichia coli* and other coliforms, and *Streptococcus uberis*. Control relies on clean, dry bedding, stall hygiene, teat preparation and dry-period management.

The therapeutic meaning is important. *S. agalactiae* is usually very sensitive to penicillins and responds well. *S. aureus* often responds poorly in established infections, because it can sit inside cells, form scar tissue, and in some strains produce beta-lactamase. Coliform mastitis is often acute with endotoxin shock; the udder frequently clears the bacteria itself, so supportive care (fluids, anti-inflammatory drugs) is the priority and the role of antibiotics depends on the severity and on the veterinarian's judgement. *Mycoplasma* lacks a cell wall, so beta-lactam antibiotics cannot work, and infected cows are usually segregated or culled. Yeasts, algae such as *Prototheca*, and some fungi do not respond to antibacterial treatment, and antibiotics may even worsen yeast infections.

Culture and antibiotic choice in lactation

Culture is the most useful tool for rational use. A properly collected, aseptic quarter sample cultured on suitable media identifies the organism. On-farm culture systems let the herd team separate quarters that need antibiotic from those that do not: for example, a gram-negative result in a mild case, or no growth at all, may mean that no antibacterial treatment is required.

Choice of drug follows three principles.

1. **Narrowest effective spectrum.** For gram-positive pathogens such as streptococci, a narrow-spectrum penicillin is usually preferred. Broad-spectrum and critically important agents, such as later-generation cephalosporins and fluoroquinolones, should be kept for cases where culture or sensitivity testing justify them.

2. **Route.** Mild clinical cases of gram-positive infection are generally treated by the intramammary route, which gives high local concentration. Severe cases with systemic signs may need parenteral therapy in addition, since the udder may not take up intramammary drug when it is badly swollen, and bacteraemia may be present.
3. **Duration.** Treatment should continue for the labelled or evidence-supported duration; stopping early encourages relapse and selection of resistant survivors.

Remember that susceptibility on a laboratory plate does not guarantee cure in the udder. Breakpoints are often derived from blood concentrations, while milk and tissue conditions differ. Cure also depends on the cow: older cows with a long infection, high somatic cell counts and multiple quarters infected cure less often.

Dry-cow therapy and teat sealants

The dry period is a key moment in the udder's cycle. New infections are most common early in involution and just before calving, when the protective keratin plug is not yet formed or is weak. Dry-cow therapy has two aims: to cure infections present at drying off, and to prevent new infections during the dry period.

Dry-cow intramammary products are formulated for a slow release and a long duration of action, because the drug is not removed by milking. Two strategies are used.

- **Blanket dry-cow therapy** treats all quarters of all cows at drying off. It is simple and effective but leads to the most antibiotic use and treats many healthy quarters.
- **Selective dry-cow therapy** treats only cows or quarters considered infected, based on records such as somatic cell counts, clinical history, culture or tests. It reduces antibiotic use but needs good records and a low-prevalence herd to avoid more new infections.

Internal teat sealants are non-antibiotic pastes, often based on bismuth subnitrate, infused into the teat canal to act as an artificial keratin plug. They prevent bacteria from entering and can be used alone in cows known to be uninfected, or together with antibiotic in cows that need treatment. A key point is that a sealant does not cure existing infection and that infusion must be hygienic. Infusing contaminated material into the teat does more harm than good.

Teat dips and the mechanism of prevention

Most mastitis control is non-therapeutic. **Post-milking teat dips** disinfect the teat skin and canal while the sphincter is still open after milking, killing bacteria that would otherwise enter. Common active agents include iodophors, chlorhexidine and other antiseptics, and emollients prevent chapping. Post-dipping mainly reduces contagious infections because it removes organisms left on the teat from milking. **Pre-milking dips** or wipes reduce environmental pathogens, and teats must be dried so that residual dip does not enter milk.

Complementary practices give the full picture: well-maintained milking machines, correct liner function, clean hands or gloves, milking infected cows last, fresh water and bedding, and good nutrition including vitamin E and selenium in the dry period to support immunity. Somatic cell counts, California Mastitis Test results and bulk-tank cultures give early warning. The value of this approach is that every infection prevented is a treatment, a discard and a residue risk avoided.

A common confusion is to treat dips as therapy. They do not cure established intramammary infection, and they are not substitutes for antibiotics in clinical cases, but they remain the best long-term way to lower antibiotic use.

Residue management and reducing antibiotic use

Every intramammary product has its own milk discard time and a separate meat withdrawal time. Because the udder tubes act locally and milk is the product, **discard times are for milk from all quarters** after systemic therapy, and from the treated cow's milk supply as a whole according to the label. Dry-cow products bring a different issue: if a cow calves early, before the minimum interval after dry treatment, her early milk may contain drug. The label gives the required interval between treatment and calving. Check the current label and rules for the specific product, since they differ between products and countries.

Practical residue steps include clear marking of treated cows, milking them last, keeping their milk out of the tank, using a screening test before a treated cow's milk returns to the vat, and keeping treatment records. Do not feed waste milk containing antibiotic to calves without recognising that it can select resistant gut bacteria.

To reduce antibiotic use:

- Prevent infection with hygiene, dips, sealants and dry-period management.
- Use culture to treat only quarters likely to benefit, and consider no antibiotic in mild gram-negative or no-growth cases.
- Use selective dry-cow therapy where herd conditions allow it.
- Cull chronic, non-responsive cows, particularly those with *Staph. aureus* or mycoplasma infection.
- Choose narrow-spectrum agents first and keep critically important antibiotics for justified cases.
- Review results regularly, since stewardship is a cycle of measuring, adjusting and measuring again.

Indian dairy practice is often smallholder-based with hand milking, and the principles are unchanged: clean milking, teat dipping, early detection, and treatment guided by culture where it is available. Check the current regulations and notifications on antimicrobial use in food animals.

Concept cleared

Treat the pathogen, not the signs
Streptococci respond to narrow-spectrum penicillin, Staph. aureus often does not, coliform mastitis needs supportive care, and Mycoplasma and yeasts do not respond to standard antibacterials.

Dry period is a prevention window
Dry-cow products cure existing infection and protect against new ones in involution, when the keratin plug is not yet fully formed.

Sealant is a barrier, not a drug
Internal teat sealants block the teat canal physically. They do not cure infection and must be infused hygienically.

Prevention is the best stewardship

Dips, milking hygiene and dry-period management reduce infections and so reduce treatments, discards and residue risk.

Memory aid: SAS for contagious

Contagious mastitis: Strep agalactiae, Staph aureus, Mycoplasma spread at milking. Environmental: E. coli and Strep uberis come from bedding. Remember: 'milking machine spreads, bedding breeds'.

Compare and contrast

Contagious and environmental mastitis

Feature	Contagious	Environmental
Examples	S. agalactiae, S. aureus, Mycoplasma	E. coli, other coliforms, S. uberis
Source	Infected udders, spread at milking	Bedding, manure, wet surroundings
Main control	Milking hygiene, post-milking dip, culling	Clean dry housing, teat preparation, dry-period care
Therapy note	Variable: streptococci respond well, S. aureus and Mycoplasma poorly	Coliform cases often need supportive care; self-cure is common

Blanket and selective dry-cow therapy

Feature	Blanket	Selective
Cows treated	All cows, all quarters	Only cows or quarters judged infected
Antibiotic use	Highest	Lower
Requirements	Few records needed	Good records, culture or cell counts, low infection prevalence
Companion measure	Sealant optional	Sealant commonly used in uninfected cows

Species notes

Cattle

Most intramammary products are licensed for cows. Follow the label discard times, and use culture and cell-count records for selective therapy.

Buffalo

Mastitis is a major problem, with narrow, long teats and hand milking in many herds. Data specific to buffalo are fewer, so use the cattle principles and check the label for buffalo use.

Goats and sheep

Mastitis often shows as subclinical infection with coagulase-negative staphylococci. Few products are licensed for them, so extra-label use requires a careful, conservative withdrawal.

Sows and mares

Sows may develop mastitis as part of the postpartum syndrome, treated mainly by systemic therapy, as intramammary infusion is not practical. Mares are rarely affected.

Dogs and cats

Mastitis occurs in lactating or pseudopregnant animals. Choose a drug that is safe for nursing young and use systemic therapy guided by culture.

Clinical pearls

Self-test: 10 questions

1. Which pathogen is least likely to respond to beta-lactam intramammary therapy?

Mycoplasma has no cell wall, so cell-wall inhibitors cannot act on it.

2. Environmental mastitis is mainly controlled by:

Environmental organisms come from bedding and manure, so hygiene is the main control.

3. The main purpose of an internal teat sealant is to:

It mimics the keratin plug and does not treat infection.

4. Selective dry-cow therapy differs from blanket therapy because it:

Selection relies on records, cell counts or culture and reduces antibiotic use.

5. Post-milking teat dipping chiefly reduces which type of infection?

It removes organisms left on the teat skin during milking while the canal is open.

6. In a mild clinical case, culture shows no growth. The most reasonable action is:

No growth often means self-cure or non-bacterial cause, so antibiotic may add nothing.

7. Why can in-vitro sensitivity fail to predict cure in the udder?

Breakpoints may not reflect udder conditions, and some organisms hide from drug.

8. Which statement about coliform mastitis is most appropriate?

Coliforms cause endotoxin-mediated illness, so fluids and anti-inflammatory drugs matter most.

9. After a treated cow completes milk discard time, what else must be checked before she is sold for slaughter?

Milk and meat withdrawals are separate figures.

10. Which approach best reduces total antibiotic use in a herd?

Preventing infection and treating only quarters likely to benefit lowers use and residues.

Key points to revise

1. Mastitis causes the largest share of antibiotic use and residue risk on dairy farms.
2. Contagious pathogens spread at milking; environmental pathogens come from bedding and manure.
3. Streptococci usually respond to penicillins; S. aureus often responds poorly.
4. Coliform mastitis often needs supportive care, with antibiotic use depending on severity.
5. Culture identifies the organism and helps avoid unnecessary treatment.
6. Dry-cow therapy cures existing infection and prevents new ones; selective therapy lowers use.
7. Teat sealants form a physical barrier; teat dips disinfect the teat skin.
8. Reduce use by prevention, culture-guided treatment, narrow-spectrum choice and culling chronic cases.

Go deeper on this site

- Ch 12. Antifungal drugs (in this book)
- Ch 10. Drug residues, MRLs and food safety (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Concepts
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual
- National Mastitis Council
- WHO, Antimicrobial resistance

CHAPTER 12 OF 19

Antifungal drugs

Fungal cells are eukaryotes, so selective toxicity depends on a few unique targets, mainly ergosterol and the cell wall. This chapter explains how azoles, polyenes, griseofulvin, terbinafine and related drugs work, how they are matched to dermatophytosis and systemic mycoses, and why toxicity, interactions and slow therapy shape clinical use.

After this chapter you can

- Explain why fungi are harder to target than bacteria and name the main antifungal targets
- Describe the mechanisms and key adverse effects of azoles, polyenes, griseofulvin and terbinafine
- Outline the principles of treating ringworm in animals, including environmental control and zoonotic risk
- Match drug classes to major systemic mycoses in veterinary practice
- Explain resistance, drug interactions and limits on antifungal use in food animals

Why antifungal selectivity is difficult

Bacteria are prokaryotes, and many antibiotics exploit structures that mammals do not have. Fungi are **eukaryotes**. Their ribosomes, DNA replication and protein synthesis are close to those of the host, so a drug that damages these processes in fungi usually damages host cells too. Useful antifungal drugs therefore target the few features that differ.

The main differences are the following.

- **Ergosterol** is the main sterol of the fungal cell membrane, while mammalian membranes use cholesterol. Both the polyenes and the azoles act through ergosterol, in different ways.

- The **cell wall**, built from glucans and chitin, is absent in mammals. Echinocandins block glucan synthesis.
- Special pathways, such as the squalene epoxidase step of ergosterol synthesis, are targeted by terbinafine.

Fungal infections are also slow, often deep and granulomatous, and affect animals with weakened defences. As a result, treatment is usually measured in weeks or months, the drugs are expensive, and relapse after stopping early is common. Cheap in-vitro testing is limited, so clinical experience and species knowledge guide the choice.

Azoles: blocking ergosterol synthesis

The azoles inhibit the fungal cytochrome P450 enzyme **lanosterol 14-alpha-demethylase**. This blocks the conversion of lanosterol to ergosterol. The membrane becomes depleted of ergosterol and accumulates abnormal sterols, so it is leaky and its enzymes work badly. The effect is mostly fungistatic.

The family has two groups: the older *imidazoles* (ketoconazole, clotrimazole, miconazole, enilconazole, many used topically) and the *triazoles* (itraconazole, fluconazole, voriconazole, posaconazole), which are more selective for fungal enzyme and are preferred for systemic use.

Features worth remembering:

- **Itraconazole** has a broad spectrum, and is lipophilic, so absorption depends on formulation and feeding. It is widely used for dermatophytes, *Malassezia*, and several systemic mycoses.
- **Fluconazole** is water-soluble, reaches the central nervous system and urine well, and is therefore useful in cryptococcal meningitis and fungal urinary infections. It is less active against moulds such as *Aspergillus*.
- **Ketoconazole** inhibits mammalian steroid synthesis, an effect used in medical treatment of some endocrine diseases but a drawback in antifungal use. Newer agents have replaced it in many settings.

Because azoles also inhibit **mammalian cytochrome P450** enzymes, they raise the levels of other drugs metabolised by the same enzymes, and they can inhibit P-glycoprotein. Hepatotoxicity is the main class adverse effect, with anorexia and

vomiting often the first signs, so liver monitoring is part of long courses. Azoles can also be teratogenic, and use in pregnancy needs caution.

Polyenes and flucytosine

Amphotericin B and **nystatin** are polyenes. They bind ergosterol in the fungal membrane and form pores, so ions and small molecules leak out and the cell dies. This is a fungicidal action. The selectivity is incomplete, because the drug also binds cholesterol to a lesser extent.

That explains the main toxicity of conventional amphotericin B, which is **nephrotoxicity**: renal tubular cells are damaged and renal vasoconstriction occurs. Careful hydration, with saline loading, and monitoring of kidney values are the usual precautions. **Lipid-based formulations** carry the drug to fungal tissue with less renal exposure, but are costly. The drug is poorly absorbed from the gut and is given by slow intravenous infusion for systemic disease. Nystatin is too toxic for systemic use and is used topically or orally for surface or gut candidiasis.

Flucytosine is a pyrimidine analogue that enters fungal cells and is converted into a fraudulent nucleotide, interfering with RNA and DNA synthesis. Resistance appears quickly when it is used alone, so it is given in combination with amphotericin B, for example in cryptococcosis. Bone marrow suppression and skin reactions are among its adverse effects.

Echinocandins such as caspofungin inhibit glucan synthase and are intravenous drugs used mostly for invasive candidiasis and aspergillosis in specialised settings. Their veterinary use is limited.

Griseofulvin and terbinafine for dermatophytes

Griseofulvin is active only against dermatophytes, and works by disrupting microtubules and mitosis in fungal cells. After oral dosing it is deposited in keratin precursor cells, so new keratin that grows is resistant to infection and the infected keratin is shed as the hair or skin renews. This explains two clinical points. Treatment takes weeks, because it must outlast the turnover of infected keratin, and the drug has no effect on non-dermatophyte fungi. Absorption improves with a fatty meal.

Griseofulvin is **teratogenic** and must not be given to pregnant animals. It can cause bone marrow suppression, with cats infected with feline immunodeficiency virus being at particular risk, and it may cause gastrointestinal upset and hepatic effects. Many clinicians now prefer other drugs, where available.

Terbinafine is an allylamine that inhibits **squalene epoxidase**, early in the ergosterol pathway. Ergosterol falls and toxic squalene accumulates inside the cell, which gives a fungicidal effect against dermatophytes. It is keratophilic, concentrating in skin, hair and nails, and has a high activity against dermatophytes but less against yeasts and many moulds. It is used to treat dermatophytosis, and is generally well tolerated, with gastrointestinal upset and occasional liver enzyme rises reported.

The topical agents, such as miconazole, clotrimazole and enilconazole, may be used as washes, creams or rinses to reduce spore load on the hair, and lime sulphur dips are an older, inexpensive topical choice.

Ringworm: treatment and control

Ringworm (dermatophytosis) is caused by keratin-loving fungi such as *Microsporum canis* in cats and dogs, *Trichophyton verrucosum* in cattle, *Trichophyton equinum* in horses and *Microsporum gypseum* from soil. In healthy animals it is usually self-limiting over weeks to months, but treatment is still given to shorten the course, to stop spread and, importantly, to protect people, because the infection is **zoonotic**.

The principles are:

1. **Confirm the diagnosis** with Wood's lamp (which detects only some strains of *M. canis*), direct microscopy of hairs and fungal culture. Do not treat on appearance alone, since other skin disease can look similar.
2. **Combine topical and systemic therapy** in companion animals: topical treatment reduces spores on the coat, while a systemic drug eliminates infection in hair follicles.
3. **Decontaminate the environment.** Spores persist for a long time on bedding, grooming tools and surfaces. Cleaning, vacuuming, and disinfection with a suitable agent are necessary, or treated animals are reinfected.

4. **Continue until cure is proven**, usually by negative cultures, not just until the lesions appear to heal.
5. **Protect people**: use gloves, wash hands, and tell owners about the risk, with particular concern for children and immunosuppressed persons.

In cattle, ringworm is common in housed young stock and tends to resolve itself. Management of crowding, hygiene, and nutrition matter more than drug use, and topical treatment of lesions is the usual approach. Check which drugs are permitted in food animals before treating them.

Systemic mycoses, resistance and cautions

Systemic mycoses are caused by fungi that invade deep tissue, often after inhalation of spores from soil or bird droppings, or when immunity is weak. Examples include **aspergillosis** (nasal and disseminated disease in dogs, and mycotic infections in birds and in bovine abortion), **cryptococcosis** (nasal, skin and nervous system disease, especially in cats), **candidiasis** (a mucosal and opportunistic yeast infection), **sporotrichosis** (a subcutaneous infection that may spread to people and cats), and the geographically restricted blastomycosis, histoplasmosis and coccidioidomycosis, which are more important in certain regions than in India. Check the local disease pattern.

Drug choice follows the organism and the site. Triazoles, particularly itraconazole and fluconazole, form the base of treatment for many infections, and amphotericin B, with or without flucytosine, is reserved for severe or life-threatening disease. Fluconazole is chosen when the drug must reach the brain or urine. Treatment commonly lasts for months and continues beyond clinical recovery.

Resistance develops by several mechanisms: mutation or over-expression of the target enzyme, efflux pumps, and biofilm formation. Under-dosing and repeated short courses promote it. Some yeasts, such as certain *Candida* species, are intrinsically less susceptible to fluconazole, so identification matters.

Finally, **food animals**. Many antifungal drugs are not authorised for animals that produce milk, meat or eggs, and withdrawal data are generally lacking, so their use is restricted. Rules differ between countries, and for India you should check the current notification before using any antifungal in a food animal.

Concept cleared

Eukaryote problem

Fungi resemble host cells, so antifungals rely on unique targets: ergosterol, the glucan cell wall and squalene epoxidase.

Two ways to attack ergosterol

Azoles stop its synthesis by inhibiting 14-alpha-demethylase, while polyenes bind the finished sterol and punch holes in the membrane.

Keratin is the target for ringworm drugs

Griseofulvin and terbinafine concentrate in keratinised tissue, so therapy lasts until infected hair or skin is replaced.

Treat the environment too

Spores persist on bedding and tools, so ringworm control needs cleaning and disinfection as well as drugs.

Memory aid: Azoles stop, polyenes pop

Azoles stop ergosterol being made. Polyenes pop holes in the membrane. Terbinafine stops squalene epoxidase, and griseofulvin sits in keratin.

Compare and contrast

Main antifungal classes

Class	Target	Effect	Key adverse effect or caution
Azoles (itraconazole, fluconazole, ketoconazole)	14-alpha-demethylase, ergosterol synthesis	Mostly fungistatic	Hepatotoxicity, P450 interactions, teratogenicity
Polyenes (amphotericin B, nystatin)	Bind ergosterol and form pores	Fungicidal	Nephrotoxicity (amphotericin B); nystatin topical only
Allylamines (terbinafine)	Squalene epoxidase	Fungicidal for dermatophytes	Gastrointestinal upset, occasional liver enzyme rise
Griseofulvin	Microtubules in dermatophytes	Fungistatic	Teratogenic, marrow suppression, dermatophytes only
Echinocandins (caspofungin)	Glucan synthase in the cell wall	Fungicidal for Candida	Intravenous only, limited veterinary use

Itraconazole and fluconazole

Feature	Itraconazole	Fluconazole
Solubility	Lipophilic	Water-soluble
Absorption	Depends on formulation and feeding	Good
Tissue reach	Skin and many tissues	Reaches brain and urine well
Spectrum	Broad, includes Aspergillus and dermatophytes	Narrower, little mould activity
Typical use	Dermatophytes, Malassezia, some systemic mycoses	Cryptococcosis, fungal urinary infection

Species notes

Dogs

Malassezia dermatitis and dermatophytosis are common. Aspergillosis affects the nasal cavity.

Cats

Microsporum canis ringworm is the typical problem and is zoonotic. Cryptococcosis and sporotrichosis

Azoles and terbinafine are used with attention to liver values and drug interactions.

occur. Griseofulvin carries a marrow risk, particularly with FIV infection.

Cattle

Trichophyton verrucosum ringworm is common in housed young animals and is mostly self-limiting. Rely on hygiene and topical care, and check drug rules for food animals.

Horses

Dermatophytosis is spread by tack and grooming gear, so equipment must be cleaned. Guttural pouch mycosis is an important mycotic disease, which is treated with specific therapy.

Birds

Aspergillosis is an important respiratory disease, especially in stressed or captive birds. Treatment is prolonged and combines antifungal drugs with improved husbandry.

Clinical pearls

Self-test: 10 questions

1. Azole antifungals act by inhibiting:

Azoles block this P450 enzyme, preventing ergosterol synthesis. Squalene epoxidase is the terbinafine target and glucan synthase is the echinocandin target.

2. The main dose-limiting toxicity of conventional amphotericin B is:

Amphotericin B damages renal tubules and causes renal vasoconstriction, so hydration and monitoring are needed.

3. Which drug is active only against dermatophytes?

Griseofulvin has no useful activity against yeasts or moulds.

4. Terbinafine is fungicidal for dermatophytes because it:

Inhibition of squalene epoxidase reduces ergosterol and squalene accumulates.

5. Which drug would you choose to reach the brain and urine in cryptococcosis?

Fluconazole is water-soluble and penetrates cerebrospinal fluid and urine well.

6. Why must griseofulvin not be given in pregnancy?

Griseofulvin can cause fetal malformations.

7. A key reason azoles cause drug interactions is that they:

Inhibition of P450 raises levels of co-administered drugs metabolised by those enzymes.

8. Which statement about ringworm control is correct?

Spores persist and cause reinfection; the disease can spread to people and Wood's lamp detects only some strains.

9. Why is flucytosine used with amphotericin B and not alone?

Rapid emergence of resistance limits its use as a single agent.

10. Polyene antifungals kill fungi by:

They bind ergosterol and make the membrane leaky.

Key points to revise

1. Fungi are eukaryotes, so antifungal drugs target ergosterol, the cell wall or squalene epoxidase.
2. Azoles inhibit lanosterol 14-alpha-demethylase and block ergosterol synthesis.
3. Polyenes bind ergosterol and form membrane pores; amphotericin B is nephrotoxic.
4. Terbinafine inhibits squalene epoxidase and is keratophilic.
5. Griseofulvin is active only against dermatophytes and is teratogenic.
6. Ringworm control needs diagnosis, topical and systemic therapy, environmental cleaning and zoonotic precautions.
7. Systemic mycoses need months of therapy, usually with a triazole, and amphotericin B for severe disease.
8. Check current rules before using antifungals in food animals.

Go deeper on this site

- Ch 13. Antiviral drugs and interferons (in this book)
- Ch 11. Mastitis and intramammary therapy (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual
- CDC, About Fungal Diseases
- WOAH, World Organisation for Animal Health

CHAPTER 13 OF 19

Antiviral drugs and interferons

Why antiviral chemotherapy is limited in veterinary practice, how the few available agents work, what interferons and other immunomodulators can and cannot do, and why supportive care and vaccination remain the backbone of managing viral disease.

After this chapter you can

- Explain why selective toxicity is hard to achieve against viruses and why few antivirals are used in animals
- Describe the mechanism of nucleoside analogues and name examples used in cats and in human medicine
- Explain what interferons are and the evidence-based place of feline interferon omega
- Distinguish true antivirals from immunomodulators and from unproven supplements
- Outline a supportive approach to viral disease, including the role of antibiotics and vaccination

Why antivirals are the weak link in chemotherapy

Bacteria are separate cells with their own ribosomes, cell walls and enzymes, so an antibiotic can strike a bacterial target that the host lacks. A virus is different. It is an obligate intracellular parasite and uses the host cell's ribosomes, energy and many enzymes to copy itself. A drug that blocks a viral step can easily harm the host cell too.

This is the problem of **selective toxicity**. Useful antivirals therefore aim at steps that are specific to the virus, such as a viral polymerase, protease, neuraminidase or an enzyme that only the virus uses to activate a drug.

Two more problems limit use in animals. First, by the time clinical signs appear, viral replication has often peaked, so a drug that only stops replication comes late. Second, most antivirals are developed and licensed for human disease. Cost, toxicity data in animal species, and the need to treat large numbers of food animals make routine use impractical.

For this reason, veterinary virology relies on prevention (vaccination, biosecurity, quarantine) far more than on treatment.

How antivirals work: the main mechanisms

Most antivirals act at one stage of the viral life cycle. Learning the stage tells you the drug class.

- **Nucleoside analogues.** These resemble the building blocks of DNA or RNA. Inside the cell they are converted to a triphosphate form and are taken up by the viral polymerase in place of the normal base. This stops chain growth or introduces errors. Aciclovir and famciclovir (a prodrug of penciclovir) work against herpesviruses. Ribavirin and the nucleoside analogue GS-441524 are used against RNA viruses.
- **Viral selectivity through activation.** Aciclovir is first phosphorylated by a viral thymidine kinase. Uninfected cells do this poorly, so the active drug builds up mainly in infected cells. This is a good example of how selectivity is achieved.
- **Neuraminidase inhibitors** such as oseltamivir block release of new influenza virus particles.
- **Protease and entry inhibitors** are used in human HIV and hepatitis medicine and have little place in veterinary work.

A common confusion: antivirals are mostly *virostatic*. They hold replication down while the immune system does the clearing. They do not remove latent virus, so herpesviruses can return after treatment is stopped.

Antivirals used in companion animals

Use in animals is narrow and mostly in cats.

Feline herpesvirus 1. Famciclovir is the systemic agent discussed in feline guidelines such as those of the ABCD (European Advisory Board on Cat Diseases). Evidence comes from experimental studies, a shelter study and field reports, and it is considered to reduce signs and shedding. Topical antivirals applied to the eye, such as ganciclovir, are used for herpetic keratitis. Treatment reduces disease but cannot cure the latent infection in the trigeminal ganglion.

Feline infectious peritonitis (FIP). This was once almost always fatal. Nucleoside analogues, notably GS-441524 and related compounds, have changed this: the

ABCD guideline describes them as curative in most cases when given with supportive care, and notes that they are not available in all countries. Legal status, licensed products and the use of unlicensed products differ between countries, so check the current position in India and the guidance of the regulator before recommending any product.

Other viruses. There is no proven specific antiviral for canine parvovirus, canine distemper, feline panleukopenia or rabies. Rabies in particular must never be approached as a treatable disease in animals. Prevention by vaccination is the only dependable approach.

Zidovudine has been used in cats with FIV, but it can cause anaemia and its use is limited to selected cases under specialist advice.

Interferons and immunomodulators

Interferons are cytokines released by infected cells. They do not attack the virus directly. They bind receptors on neighbouring cells and switch on genes that make those cells resistant to infection, and they also help natural killer cells and T cells. This is the body's first antiviral line, which is why interferon is described as an *immunomodulator* and not a classic antiviral.

Feline interferon omega is licensed in some countries for cats and also for dogs with parvovirus in some regions. Feline guidelines call it safe, but the evidence for benefit in herpesvirus and calicivirus disease is limited. Human recombinant interferon alpha given by mouth is an old practice with weak evidence, and antibodies may develop against foreign interferon on repeated injection.

Other immunomodulators. Products such as inactivated bacterial or *Propionibacterium* preparations, acemannan and similar compounds are marketed to stimulate immunity. Evidence is mostly weak or anecdotal. Treat claims with caution and prefer products with controlled studies.

L-lysine is often given to cats with herpesvirus. The ABCD guideline states that there is no evidence of efficacy, and that it may even carry a risk of arginine deficiency in kittens. Students should know this as a well-known myth.

Supportive care: the real treatment

Since most viral diseases have no specific cure, good supportive care often decides the outcome.

- **Fluids and electrolytes.** Correct dehydration and acid-base disturbance, especially in vomiting and diarrhoea such as parvovirus enteritis.
- **Nutrition.** Early feeding, warmed palatable food, appetite stimulants and a feeding tube if the animal has not eaten for several days are all supported in feline guidelines.
- **Symptomatic relief.** Antiemetics, analgesia, nebulisation and cleaning of discharges. NSAIDs should be used only after hydration is restored.
- **Secondary bacterial infection.** Antibiotics do nothing to the virus. They are given only when a bacterial complication is suspected. This matters for stewardship: giving antibiotics for every viral fever adds to resistance without benefit.
- **Isolation and hygiene.** Separate infected animals, disinfect with agents effective against the virus and notify where a disease is reportable.

Corticosteroids can suppress the immune response and may worsen viral disease, so their use must be a deliberate decision.

Livestock, poultry and prevention

In food animals, antiviral drugs are not used as routine therapy. Foot and mouth disease, peste des petits ruminants, lumpy skin disease, Newcastle disease and bird flu are controlled by vaccination, movement control, culling or stamping out where policy requires, and biosecurity. Antibiotics may be needed for secondary infections in these outbreaks, which brings the usual residue and withdrawal responsibilities.

Antiviral drugs used in human medicine, such as oseltamivir, are a stewardship concern in animals because resistance in animal viruses could affect human treatment. Official bodies in many countries restrict this use. Check the current notifications of the Indian regulator before any such use.

For the clinician, the correct order of thought is: prevent by vaccine, confirm the diagnosis, give supportive care, and use a specific antiviral only when evidence and the law allow. Vaccination failures are mostly due to maternal antibody interference,

broken cold chain or exposure before immunity develops, and the veterinarian should look for these before blaming the vaccine.

Concept cleared

Selective toxicity is the central problem
Viruses use host machinery, so antivirals must target virus-specific enzymes or virus-specific activation steps to spare the host.

Nucleoside analogues
They are phosphorylated to a triphosphate and incorporated by viral polymerase, causing chain termination or errors. Aciclovir relies on viral thymidine kinase for selectivity.

Virostatic, not virucidal
Most antivirals suppress replication while immunity clears the virus. They do not eliminate latent herpesvirus.

Interferon is an immunomodulator
Interferons induce an antiviral state in neighbouring cells and boost immune cells. They do not act on the virus directly.

Memory aid: SIVA for viral disease management
Support, Isolate, Vaccinate, Antiviral only if proven. The order tells you where most of the effort should go.

Compare and contrast

True antivirals versus immunomodulators

Feature	Antiviral drug	Immunomodulator
Target	Viral enzyme or replication step	Host immune response
Examples	Famciclovir, aciclovir, GS-441524	Interferon omega, acemannan
Evidence in animals	Good for a few diseases (FHV-1, FIP)	Mostly limited or variable
Main limit	Narrow spectrum, availability, legal status	Weak evidence, antibody formation

Antibiotic versus antiviral logic

Feature	Antibiotic	Antiviral
Pathogen biology	Own cell structures	Uses host cell machinery
Selectivity	High	Difficult
Effect on virus	None	Usually virostatic
Role in viral illness	Only for secondary bacterial infection	Specific agents only for a few viruses

Species notes

Cat
The main species for antiviral use: famciclovir for herpesvirus, nucleoside analogues for FIP where legally available. Avoid lysine as an antiviral. Be careful with any human drug in cats because of species-specific toxicity.

Dog
No proven specific antiviral for parvovirus or distemper. Supportive fluid and nutrition care and vaccination are the basis of management.

Cattle, buffalo, sheep and goat
Antivirals are not used. Control relies on vaccination programmes and movement control. Antibiotics only

Poultry
No antiviral therapy. Vaccination and biosecurity prevent outbreaks. Antibiotic use for secondary

treat secondary infections, with withdrawal periods respected.

infection should follow stewardship and residue rules.

Horse

Antivirals such as aciclovir or valaciclovir are sometimes discussed for equine herpesvirus, but evidence is limited. Isolation and supportive care remain essential.

Clinical pearls

Self-test: 10 questions

1. Why is selective toxicity difficult for antiviral drugs?

Because viruses replicate inside host cells using host machinery, drugs that block replication can harm host cells.

2. Aciclovir is selectively activated in infected cells by:

Viral thymidine kinase phosphorylates aciclovir far better than host enzymes.

3. Famciclovir is mainly used in cats against:

Famciclovir is a penciclovir prodrug used for herpesvirus infection.

4. Interferons are best described as:

They act on host cells, not directly on the virus.

5. The status of L-lysine for feline herpesvirus according to feline guidelines is:

The ABCD guideline states there is no evidence of efficacy.

6. Antibiotics in a cat with viral upper respiratory disease are justified when:

Antibiotics do not act on viruses; they are for bacterial complications.

7. Most antivirals are best described as:

They suppress replication while immunity clears the virus.

8. Which statement about FIP treatment is most accurate?

Feline guidelines describe nucleoside analogues as curative and note they are not available in all countries.

9. Which is the foundation of controlling viral disease in livestock?

Antivirals are not routinely used in food animals; prevention is key.

10. Oseltamivir blocks which step in influenza virus replication?

It is a neuraminidase inhibitor.

Key points to revise

1. Viruses depend on host cells, so selective toxicity is hard to achieve.
2. Few antivirals are licensed or proven in animals.
3. Nucleoside analogues act on viral polymerase after phosphorylation.
4. Aciclovir selectivity depends on viral thymidine kinase.
5. Antivirals are mostly virostatic and do not remove latent virus.
6. Interferons are cytokines that induce an antiviral state and are immunomodulators.
7. Supportive care and vaccination are the foundation of managing viral disease.

8. Check current Indian notifications before using or recommending antivirals in animals.

Go deeper on this site

- Ch 14. Anthelmintics (in this book)
- Ch 12. Antifungal drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- ABCD Cats Vets: Feline herpesvirus guideline
- ABCD Cats Vets: Feline infectious peritonitis guideline
- Merck Veterinary Manual: Pharmacology

CHAPTER 14 OF 19

Anthelmintics

The main anthelmintic classes, their molecular targets and spectrum, how resistance develops, and how targeted selective treatment such as the FAMACHA system slows it. Residue and withdrawal logic and stewardship are emphasised.

> **After this chapter you can**
>
> - State the mechanism and spectrum of benzimidazoles, imidazothiazoles, macrocyclic lactones, salicylanilides and praziquantel
> - Explain why each class is selective for the parasite
> - Describe how anthelmintic resistance arises and the concept of refugia
> - Explain FAMACHA and targeted selective treatment in small ruminants
> - Apply residue, withdrawal and stewardship principles to anthelmintic use

Principles of anthelmintic therapy

Helminths are multicellular parasites, so some of their biochemistry resembles ours. Anthelmintics are useful because they exploit small differences: a parasite protein

that binds the drug more tightly than the host protein, a receptor present only in worms, or a metabolic pathway worms rely on and the host does not.

Three questions help in choosing a drug: which worm (nematode, cestode or trematode), which life stage (adult, larval, inhibited larvae), and which species and product type (food animal, pet, lactating animal). No single class covers every worm, so the **spectrum** of each class must be known.

Modern use is also shaped by resistance. Because nearly all drug classes have lost effect in some parasite populations, the goal is no longer to kill every worm but to keep animals productive while preserving drug efficacy.

Benzimidazoles and imidazothiazoles

Benzimidazoles (for example albendazole, fenbendazole, oxfendazole) bind parasite beta-tubulin and prevent microtubule formation. Cell division, nutrient absorption and transport inside the worm fail. They are selective because they dissociate much more slowly from parasite tubulin than from mammalian tubulin. They have a broad spectrum against nematodes, and some also act on cestodes and the fluke Fasciola (albendazole). Many have action against eggs and larvae. Albendazole has caused concern in early pregnancy because of teratogenic potential, so label cautions must be read.

Resistance to benzimidazoles is mostly due to changes in the beta-tubulin gene, so the drug binds less well. Because the change is class-wide, resistance to one benzimidazole usually means resistance to all. This is **side resistance**.

Imidazothiazoles (levamisole and the tetrahydropyrimidines such as pyrantel and morantel) are agonists at the nematode nicotinic acetylcholine receptor. The worm muscle first contracts and then undergoes depolarising block, giving spastic paralysis, and the worm is expelled. Levamisole is active against nematodes only. It has a narrower safety margin than many other classes and signs of overdose resemble cholinergic stimulation.

Macrocyclic lactones

The macrocyclic lactones include the avermectins (ivermectin, doramectin, abamectin, eprinomectin) and the milbemycins (moxidectin, milbemycin oxime). They bind **glutamate-gated chloride channels** in nematode and arthropod nerve

and muscle cells. Chloride enters, the cell hyperpolarises and the worm is paralysed, including its pharyngeal pumping.

The spectrum is wide for nematodes and for arthropods such as mites, lice and some ticks, which is why these drugs are called *endectocides*. They have no useful action against cestodes and trematodes, which appear to lack the target. They are very potent and are active at tiny concentrations.

Safety rests on two facts: mammals have these channels only in the central nervous system, and the blood-brain barrier normally keeps the drug out through the P-glycoprotein pump. Some dogs, such as collie breeds with an MDR1 (ABCB1) mutation, have a defective pump and may develop neurotoxicity. Young animals and some species may also have a less complete barrier.

Macrocyclic lactones are highly lipid soluble, remain in fat and persist in the body. This has two consequences: long protection in some products, and long meat and milk withdrawal times. Persistence also means that low concentrations remain for weeks, exposing worms to sub-lethal drug and favouring resistance. Dung from treated animals can also harm dung beetles.

Salicylanilides, flukicides and praziquantel

Salicylanilides (closantel, rafoxanide, niclosamide) and the related nitrophenols uncouple oxidative phosphorylation in the worm's mitochondria. ATP generation collapses and the parasite dies. Closantel and rafoxanide are strongly bound to plasma protein, so blood-feeding parasites such as Haemonchus and the adult liver fluke ingest high drug levels. They are therefore useful for haemonchosis and for fascioliasis in older stages. Niclosamide acts on tapeworms in the gut. Closantel has a narrow safety margin and a long persistence, so correct dosing, species rules and the label are essential.

Other flukicides such as triclabendazole are valued because they act on both immature and adult flukes, while many other drugs kill only adults. The stage of the fluke at treatment therefore decides the choice.

Praziquantel is the main cestocide and also acts on many trematodes. It disrupts calcium homeostasis in the parasite. Muscle contracts, the tegument becomes vacuolated and the worm is damaged and exposed to host immunity. It is not active against nematodes, so combination products pair it with a nematode drug.

Praziquantel will treat *Dipylidium* and *Taenia* species in dogs and cats. Control of *Echinococcus* in dogs matters for human health because of hydatid disease.

Resistance, refugia and FAMACHA

Resistance genes are usually present at low frequency before a drug is ever used. Each treatment kills susceptible worms and lets resistant ones survive and breed, so over time the resistant fraction rises. The mechanisms include changes in the drug target (beta-tubulin, receptor subunits), reduced drug uptake and increased efflux or metabolism. Resistance within a class is typically shared.

Refugia are the worms not exposed to the drug, such as larvae on pasture or worms in untreated animals. They carry susceptible genes and dilute the resistant ones. Treating every animal at every dose-day leaves little refugia and speeds resistance.

Targeted selective treatment (TST) keeps refugia by treating only animals that need it. In small ruminants, the **FAMACHA** chart compares the colour of the lower eyelid mucous membrane with a printed scale, which estimates anaemia caused by the blood-sucking nematode *Haemonchus contortus*. Only animals with scores indicating clinical anaemia are treated. Other tools include body condition score, the dag score and faecal egg counts.

FAMACHA is useful only where Haemonchus is the main problem. It will not detect other worms that do not cause anaemia, and staff need training. Good practice also includes checking efficacy after treatment, for example with a faecal egg count reduction test, quarantine dosing of new animals, and avoiding underdosing by weighing animals or dosing for the heaviest in the group only when label allows.

Residues, withdrawal and stewardship

Anthelmintic residues in meat and milk are a food safety matter. Withholding periods depend on the drug, species, route and formulation and are set by regulators, so the product label and the current Indian notifications must be checked and followed. Meat and milk are separate: a drug may need a long meat withdrawal and be barred altogether in milk-producing animals. Examples in international guidance include closantel being prohibited for dairy animals and some drugs not being authorised for lactating animals. In India, the allowed

products and limits for residues should be checked in the current notification of the regulators.

Stewardship in practice means these points:

- Use a drug only when the animal or herd needs it, based on signs, FAMACHA or egg counts.
- Choose the class by the target parasite and its known local resistance.
- Avoid frequent rotation without monitoring and avoid routine whole-herd dosing.
- Do not use extralabel products in food animals without official guidance.
- Combine drug use with pasture management, rotational grazing and good nutrition.

Remember that a good clinical response does not prove susceptibility. Confirm with a faecal egg count reduction test when resistance is suspected.

Concept cleared

Class decides spectrum
Benzimidazoles and levamisole mostly kill nematodes, macrocyclic lactones cover nematodes and arthropods, salicylanilides target blood feeders and flukes, and praziquantel targets cestodes and trematodes.

Selectivity comes from target differences
Benzimidazoles bind parasite tubulin more tightly, macrocyclic lactones need invertebrate glutamate-gated channels, and mammalian CNS channels are protected by the blood-brain barrier.

Refugia slow resistance
Untreated worms keep susceptible genes in the population. Treating only animals that need it preserves them.

Side resistance

Resistance to one drug in a class usually extends to other members because they share the target.

Memory aid: Targets: TNG-CP

Tubulin (benzimidazoles), Nicotinic receptor (levamisole), Glutamate chloride channel (macrocyclic lactones), Calcium (praziquantel); Proton uncouplers (salicylanilides) as the remaining one.

Compare and contrast

Anthelmintic classes at a glance

Class	Target	Main spectrum
Benzimidazoles	Beta-tubulin	Nematodes, some cestodes and flukes
Imidazothiazoles	Nicotinic ACh receptor agonist	Nematodes
Macrocyclic lactones	Glutamate-gated chloride channels	Nematodes and arthropods
Salicylanilides	Uncoupling of oxidative phosphorylation	Haemonchus, flukes, tapeworms (niclosamide)
Praziquantel	Calcium homeostasis	Cestodes and trematodes

Blanket treatment versus targeted selective treatment

Feature	Blanket treatment	Targeted selective treatment
Animals treated	All	Only those needing it
Refugia	Small	Large
Resistance selection	Strong	Slower
Requirement	None	Monitoring tools and trained staff

Species notes

Sheep and goat

Haemonchus contortus is the major problem in hot humid regions and resistance is widespread. FAMACHA and faecal egg counts guide treatment. Goats often need different handling of dose and metabolism than sheep, so follow label and expert advice.

Cattle and buffalo

Calves are most affected by roundworms. Fluke control depends on local snail habitat. Milk and meat withdrawal rules must be checked before using any product.

Dog and cat

Praziquantel is used for tapeworms. Macrocyclic lactones carry a risk in dogs with the MDR1 mutation. Roundworm control in puppies and kittens has a zoonotic importance.

Horse

Resistance of small strongyles to benzimidazoles is common and cyathostomin resistance to other classes is being reported. Egg counts help select animals to treat.

Poultry and pig

Roundworm control relies on benzimidazoles, levamisole or piperazine in some countries. Withdrawal rules apply to meat and eggs.

Clinical pearls

Self-test: 10 questions

1. Benzimidazoles act by binding:

They prevent microtubule formation in the parasite.

2. Levamisole produces:

It acts as a nicotinic agonist on worm muscle.

3. Macrocyclic lactones are NOT effective against:

Cestodes and trematodes appear to lack the target channel.

4. The main target of praziquantel is:

It disrupts calcium and damages the tegument.

5. Closantel and rafoxanide act by:

They are salicylanilide uncouplers.

6. Refugia refers to:

Refugia dilute resistance genes.

7. FAMACHA is used to assess:

It scores eyelid mucous membrane colour.

8. Dogs with MDR1 mutation are at special risk with:

A defective P-glycoprotein pump lets the drug into the brain.

9. Resistance across drugs of the same class is called:

Shared targets give shared resistance.

10. Which statement on withdrawal is most correct?

Withholding periods depend on drug, route, species and local regulation.

Key points to revise

1. Benzimidazoles bind beta-tubulin.
2. Levamisole is a nicotinic agonist causing spastic paralysis.
3. Macrocyclic lactones open glutamate-gated chloride channels causing flaccid paralysis.
4. Salicylanilides uncouple oxidative phosphorylation.
5. Praziquantel disturbs calcium and acts on cestodes and trematodes.
6. Resistance is selected by repeated treatment and refugia delay it.
7. FAMACHA targets treatment in small ruminants infected with Haemonchus.
8. Withdrawal rules differ for meat and milk; check the current Indian notification.

Go deeper on this site

- Ch 15. Ectoparasiticides, insecticides and acaricides (in this book)
- Ch 13. Antiviral drugs and interferons (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Anthelmintics
- Merck Veterinary Manual: Mechanisms of Anthelmintic Action
- Merck Veterinary Manual: Withholding Periods After Anthelmintic Treatment

CHAPTER 15 OF 19

Ectoparasiticides, insecticides and acaricides

Mechanisms, uses and toxicity of organophosphates, pyrethroids, amitraz, macrocyclic lactones and isoxazolines; how dips and pour-ons deliver drug; and why tick resistance and residues demand integrated control and stewardship in India.

After this chapter you can

- Explain the mechanism of organophosphates, pyrethroids, amitraz, macrocyclic lactones and isoxazolines
- Describe key toxicities, including organophosphate poisoning with its antidote and permethrin toxicity in cats
- Compare dips, sprays, pour-ons and spot-ons as delivery systems
- Explain how acaricide resistance develops in ticks and why it is a concern in India
- Apply residue, withdrawal and integrated tick control principles

Why ectoparasite control matters

Ticks, mites, lice, fleas and flies cause direct harm through blood loss, skin damage, worry and reduced production. They are also vectors of serious diseases such as babesiosis, theileriosis and anaplasmosis in cattle, and tick-borne disease in dogs. In India, tick-borne disease is a major cause of loss in cattle and in crossbred and exotic breeds in particular.

Ectoparasiticides are drugs applied to, or absorbed by, the animal so that the parasite is killed when it feeds or contacts the drug. The terms are used loosely: an **insecticide** kills insects, an **acaricide** kills ticks and mites, and a drug active against both is often called an ectoparasiticide.

Most agents are neurotoxins for the parasite. Selectivity is partly based on receptor differences, partly on the fact that the parasite receives a high dose relative to its body size, and partly on how the drug is delivered. Because the margin of safety is limited, toxicity in the host and in the environment must always be considered.

Organophosphates and amitraz

Organophosphates (OP; for example coumaphos, diazinon, chlorpyrifos) inhibit acetylcholinesterase. Acetylcholine builds up at synapses and the parasite suffers continuous stimulation and then paralysis. The binding is persistent, in contrast to the reversible binding of carbamates. The same mechanism harms mammals, so the safety margin is narrow.

Poisoning produces the muscarinic signs often remembered as SLUDGE or the DUMBELS group (salivation, lacrimation, urination, defecation, miosis, bradycardia, bronchoconstriction), nicotinic signs (muscle fasciculations, weakness) and central signs. **Atropine** blocks the muscarinic effects, and oximes such as pralidoxime may reactivate the enzyme if given early, before the enzyme-drug complex ages. Do not treat OP poisoning with atropine alone and expect nicotinic signs to resolve. Avoid using two cholinesterase inhibitors together, since effects add.

Amitraz is a formamidine that acts on octopamine receptors of mites and ticks, causing over-excitation and detachment. In mammals it can act on alpha2-adrenergic receptors and cause sedation, bradycardia and hyperglycaemia, and signs are reversed by an alpha2 antagonist such as atipamezole or yohimbine. Amitraz is toxic in horses and must not be used on them, and it should not be used on cats. Amitraz is widely used in cattle dips and sprays and in tick collars for dogs.

Pyrethroids and macrocyclic lactones

Pyrethrins are natural extracts from chrysanthemum flowers, and **pyrethroids** (permethrin, cypermethrin, deltamethrin, flumethrin) are synthetic, more stable analogues. They hold the voltage-gated sodium channels of parasite axons open, so nerve membranes depolarise repeatedly and the parasite is paralysed. The effect is quick, which gives a *knock-down* effect, and some compounds also repel parasites. Synergists such as piperonyl butoxide block parasite detoxifying enzymes and raise the effect.

Mammals are relatively safe because their sodium channels are less sensitive and they metabolise pyrethroids rapidly. **Cats** are a major exception. They are poor at glucuronidation, and spot-on products made for dogs that contain permethrin can cause tremor and seizures in cats. Cats may also be poisoned by contact with a treated dog. Pyrethroids are very toxic to fish and bees, so disposal of dip wash must be controlled.

Macrocyclic lactones such as ivermectin and doramectin act on glutamate-gated chloride channels of nematodes and arthropods, causing flaccid paralysis. They are effective against mites, lice and some ticks, and are used by injection or pour-on in livestock. Because they persist in fat, withdrawal periods in meat and milk can be long, and some products are not suitable for lactating animals.

Isoxazolines and other newer agents

Isoxazolines (afoxolaner, fluralaner, sarolaner, lotilaner) are antagonists of arthropod GABA-gated chloride channels, and of glutamate-gated channels. They block chloride entry and cause hyperexcitation and death of fleas and ticks that feed on the treated animal. Selectivity is good because affinity for mammalian GABA receptors is much lower. They give weeks of protection after a single oral or topical dose, and a parasite dies after it bites, so disease transmission may still occur in the short interval before death.

Neurological signs such as tremor, ataxia and seizures have been reported in some dogs and cats, and regulators in some countries advise caution in animals with a history of seizures. Read the current label before use in such animals.

Other agents include **neonicotinoids** (imidacloprid, nitenpyram), which act on insect nicotinic receptors, **fipronil**, a phenylpyrazole that blocks GABA channels, **spinosyns**, and **insect growth regulators** such as methoprene and lufenuron, which interrupt development of eggs and larvae. Insect growth regulators do not kill adult fleas, so they work best along with an adulticide and treatment of the environment. Fipronil is not appropriate for rabbits.

Dips, sprays, pour-ons and spot-ons

The delivery system decides how the drug is distributed, how long it acts and what risks arise.

- **Dips and sprays** wet the whole animal. In a dip, the concentration of the bath falls as animals carry out the liquid and as dirt accumulates, so the dip must be maintained and replenished as recommended, or it will under-dose parasites and select for resistance. Dip wash and spray waste are environmental pollutants and must be disposed of safely.
- **Pour-ons and spot-ons** are applied to the skin and spread by the oily layer or are absorbed. They are simple, but underdosing from estimating weight is common. Some pour-ons of macrocyclic lactones work better against lice than equivalent injections.
- **Systemic oral and injectable products** kill parasites that feed on the animal.
- **Collars and ear tags** release drug slowly. Persistent low levels expose parasites to sub-lethal concentrations over time, which favours resistance in the biting fly

and tick populations.

Operators must wear protection, particularly with organophosphates, and animals must not lick treated areas. Do not treat young, sick or debilitated animals without label advice.

Tick resistance in India, residues and integrated control

Resistance has been recorded in ticks, flies and lice to almost every class of ectoparasiticide. The tick *Rhipicephalus (Boophilus) microplus* is the best known example and has developed resistance to organophosphates, pyrethroids and amitraz in several regions. Indian studies have reported resistance in cattle ticks to some of these classes. The picture varies by region and by farm, so local susceptibility testing is the sound basis for choosing a drug. Check the current literature and state veterinary advice for your area.

Resistance mechanisms include target-site mutations (for example in sodium channels for pyrethroids and in acetylcholinesterase for organophosphates), increased detoxification enzymes and reduced penetration. Resistance is promoted by underdosing, diluted dips, frequent treatment and use of one class only. A tick has a short generation time and one host is used for all stages in the one-host tick, so selection is strong.

Integrated control reduces dependence on chemicals. It includes pasture rotation, rest of paddocks, breeding for tick resistance, good nutrition, hygiene and shed management, strategic rather than constant treatment, monitoring of efficacy, and where available, anti-tick vaccines as supplements. Rotation between classes must follow resistance results, not habit.

Residues. Ectoparasiticides given to dairy and meat animals can leave residues in milk and tissues. Withdrawal periods and permitted residue limits are set by regulators. Always read the label and check the current notifications of the Indian regulators before use, especially in lactating animals. Also note that organophosphate and pyrethroid dips pose risks to farm workers and to aquatic life.

Concept cleared

Most agents are parasite neurotoxins

Organophosphates inhibit cholinesterase, pyrethroids hold sodium channels open, amitraz stimulates octopamine receptors and isoxazolines block GABA-gated chloride channels.

Selectivity is relative

It depends on receptor differences, dose per body size and metabolism. Cats with permethrin and horses with amitraz show where it fails.

Underdosing breeds resistance

Diluted dips, weak pour-ons and constant low drug levels select resistant ticks.

Chemicals are only one part of control

Integrated control uses pasture management, breeding, hygiene, monitoring and vaccines to reduce acaricide pressure.

Memory aid: OP poisoning: DUMBELS

Defecation, Urination, Miosis, Bradycardia, Emesis, Lacrimation, Salivation. Treat with atropine for these muscarinic signs, plus an oxime if early.

Compare and contrast

Main ectoparasiticide classes

Class	Mechanism	Key caution
Organophosphates	Inhibit acetylcholinesterase	Narrow safety margin; atropine and oximes for poisoning
Pyrethroids	Keep sodium channels open	Toxic to cats (permethrin), fish and bees
Amitraz	Octopamine receptor agonist	Avoid in horses and cats; sedation in mammals
Macrocyclic lactones	Glutamate-gated chloride channels	Long withdrawal; MDR1 dogs; milk restrictions
Isoxazolines	Block arthropod GABA-gated chloride channels	Caution with seizure history per label

Dip versus pour-on

Feature	Dip or spray	Pour-on or spot-on
Coverage	Whole body wetted	Spread from application site
Main risk	Bath dilution, waste disposal	Underdosing from weight guess
Operator exposure	Higher	Lower but still present
Resistance risk	High if bath weak	High if dose is low

Species notes

Cattle and buffalo

Rhipicephalus microplus is the key tick. Dips, sprays and pour-ons are used. Resistance testing, withdrawal in milk and meat and integrated control are needed. Crossbred cattle are more susceptible than indigenous Bos indicus.

Dog

Isoxazolines, pyrethroids and amitraz collars are common. Watch for seizure history with isoxazolines and MDR1 sensitivity with macrocyclic lactones. Keep treated dogs away from cats if permethrin is used.

Cat

Horse

Very sensitive to permethrin and other insecticides. Use only products labelled for cats. Do not use amitraz.

Amitraz is contraindicated. Pyrethroid and macrocyclic lactone products must follow the label.

Sheep, goat and poultry

Dips and sprays control lice, keds and mites in sheep and goats. In poultry, mites and lice need treatment of both birds and shed. Check egg and meat withdrawal rules.

Clinical pearls

Self-test: 10 questions

1. Organophosphates act by:

They cause acetylcholine accumulation.

2. Which drug is used to treat the muscarinic signs of OP poisoning?

Atropine blocks muscarinic receptors.

3. Pyrethroids act on:

They delay channel closure in parasite nerves.

4. Which species is especially sensitive to permethrin?

Cats have poor glucuronidation and develop tremor and seizures.

5. Amitraz acts on:

It is a formamidine octopamine agonist.

6. Sedation from amitraz in mammals is reversed by:

It acts at alpha2 receptors, so an alpha2 antagonist reverses it.

7. Isoxazolines are antagonists of:

They block chloride entry in arthropod neurons.

8. Which practice most promotes tick resistance?

Sub-lethal exposure selects resistant ticks.

9. Insect growth regulators such as methoprene:

They are not adulticides.

10. Before using an acaricide in a lactating dairy animal, the vet should:

Residue limits and withdrawal periods are regulated and vary by product.

Key points to revise

1. Organophosphates inhibit acetylcholinesterase irreversibly in practice.
2. Pyrethroids prolong sodium channel opening in parasite nerves.
3. Amitraz acts on octopamine receptors and can sedate mammals.
4. Isoxazolines block arthropod GABA-gated chloride channels.
5. Cats are highly sensitive to permethrin.

6. Dips need correct concentration and replenishment.
7. Tick resistance in India varies by region; test locally and avoid underdosing.
8. Residue limits and withdrawal periods must be checked in current Indian notifications.

Go deeper on this site

- Ch 16. Antiprotozoal drugs (in this book)
- Ch 14. Anthelmintics (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Ectoparasiticides
- Merck Veterinary Manual: Ectoparasiticides Used in Large Animals
- Merck Veterinary Manual: Ectoparasiticides Used in Small Animals

CHAPTER 16 OF 19

Antiprotozoal drugs

How drugs act against the protozoa that matter in Indian veterinary practice: coccidia, Babesia, trypanosomes, Theileria and Histomonas. The chapter stresses mechanism, spectrum, resistance, residue logic and stewardship rather than doses.

After this chapter you can

- Distinguish ionophores from chemical coccidiostats by mechanism and by their main safety problems
- Explain why coccidiostats are given as prophylaxis and how resistance, rotation and vaccination fit together
- Name the main babesicides and trypanocides and explain curative versus prophylactic use
- Describe the place of buparvaquone in theileriosis and why early treatment matters

- Explain why drug choices for histomoniasis are limited and why prevention dominates

Why protozoa need special drugs

Protozoa are single-celled eukaryotes. Their cells resemble host cells more than bacteria do, so antibacterials such as penicillin are useless against them. Antiprotozoal drugs must therefore find a pathway that the parasite needs and the host lacks or uses differently. Examples are thiamine uptake, folate synthesis, mitochondrial electron transport and the unusual kinetoplast DNA of trypanosomes.

Coccidiostats: ionophores and chemical agents

Coccidiosis is caused by *Eimeria* in poultry and ruminants and by *Cystoisospora* in pups and piglets. The parasite multiplies in gut epithelium. Most damage is done by the time signs appear, so control relies on **prophylaxis**: the drug is placed in feed or water before disease develops. A drug that only suppresses development while immunity builds is called a **coccidiostat**; one that kills the parasite is a coccidiocide. Many agents behave as either depending on exposure.

Ionophores (monensin, salinomycin, lasalocid, narasin, maduramicin) form complexes with sodium, potassium and calcium and carry them across the parasite membrane. Ion balance and water content are lost and the parasite swells and dies. They act on extracellular stages, especially sporozoites and early merozoites, and allow some low-level infection that helps natural immunity. Horses are highly sensitive to ionophores, and accidental feeding of poultry or cattle feed to horses, or overdosed mixing, is a classic cause of cardiac and skeletal muscle damage. Ionophore-treated feed must never be given to horses or to species not named on the label.

Chemical coccidiostats work on specific steps:

- **Amprolium** is a thiamine (vitamin B1) analogue. It blocks parasite thiamine uptake. It is widely used in water during outbreaks, but its spectrum covers some Eimeria species poorly.
- **Sulfonamides** (sulfaquinoxaline, sulfadimidine and others), often with a folate partner, block folate-dependent nucleic acid synthesis. They are used for outbreaks, and resistance is widespread.

- **Diclazuril and toltrazuril** (triazine-type agents) act on intracellular development stages and are used in poultry, calves, lambs and piglets according to species and label.

A common confusion is that sulfonamides or amprolium are the best choice for everything. They are mainly outbreak drugs. Routine prevention in intensive flocks uses ionophores or other feed agents.

Resistance, rotation, vaccines and residues in coccidiosis

Continuous use of one anticoccidial selects resistant Eimeria strains. Two main strategies are used to slow this. In a **rotation** programme the drug is changed between flocks or at set intervals. In a **shuttle** programme one drug is used in starter feed and another in grower feed within the same flock. Sensitivity testing in a laboratory can show which products still work on a particular farm.

Live oocyst vaccines are an alternative. Low doses of sporulated oocysts give controlled infection, and immunity is largely T-cell mediated and species-specific. Vaccination is common for breeders and layers, which need long-lasting immunity.

Residue logic. Feed additives pass into tissues, so most carry a **withdrawal period** before slaughter, and several are banned in laying birds whose eggs are for human consumption. Withdrawal feed must be truly free of the drug. Residue limits and approved uses differ between countries; the current Indian rules, including any restrictions on use in layers, should be checked in the current notification of the regulator.

Babesicides

Babesia and *Theileria* are both tick-borne, but Babesia multiplies in red cells, causing haemolysis, fever, haemoglobinuria and anaemia. Two babesicides remain in common use for cattle and other animals.

- **Diminazene aceturate** is an aromatic diamidine. It is believed to interfere with parasite DNA and is also active against trypanosomes. It is given as a single injection. Dogs and camels are particularly sensitive and nervous signs from overdose can occur, so the label dose must be followed exactly.
- **Imidocarb dipropionate** works through a mechanism that is not fully understood and is active against Babesia. At higher labelled use it can give protection for

some weeks and may help clear carrier states. It has anticholinesterase effects, and salivation, tremors or colic may appear.

Important clinical points: some species do not respond well. *Babesia gibsoni* in dogs and *Babesia felis* in cats are poorly handled by ordinary babesicides. Supportive care, such as fluids, transfusion for severe anaemia and anti-inflammatory drugs, can save life while the parasite is being treated.

Trypanocides: curative and prophylactic use

In India the important trypanosome is *Trypanosoma evansi*, which causes **surra** in horses, camels, cattle, buffalo and dogs. It is mechanically transmitted by biting flies, so tsetse is not involved. African trypanosomiasis (tsetse-borne) uses the same drug classes.

- **Diminazene aceturate** is mainly curative. It leaves the body fairly rapidly and gives little long protection.
- **Isometamidium chloride** is curative and also gives prophylaxis for weeks to months because it persists in tissues. This long depot effect is its advantage and its danger: residual sub-therapeutic levels select for resistance.
- **Quinapyramine** salts are used in horses, camels, pigs and dogs. The sulfate form is curative and the less soluble form is used for prophylaxis.
- **Suramin** is given by the intravenous route in horses, camels and dogs. It is a polyanion that blocks trypanosome enzymes. It does not enter the brain well, so it cannot cure late central nervous system infection.

Most trypanocides have a **narrow therapeutic index**, so correct dosing, deep injection and correct weight estimation matter. **Resistance** develops and cross-resistance occurs, for example between diminazene and isometamidium in some parasite populations. The sanitised-treatment idea, in which a curative drug that has no long persistence is used to clear parasites before a prophylactic drug is given, is intended to reduce resistance selection.

Anti-theilerials and histomonostats

Theileriosis. *Theileria annulata* (tropical theileriosis) is a major cause of loss in crossbred cattle in India, and *T. parva* causes East Coast fever in Africa. The parasite invades lymphocytes and macrophages and transforms them so that

infected cells multiply with the host cell. Destroyed lymphoid tissue and anaemia follow.

Buparvaquone, a hydroxynaphthoquinone, is the key drug. It is believed to inhibit the parasite mitochondrial electron transport chain (cytochrome b). It is most effective when started **early**, before extensive lymphoid and haematopoietic damage. In advanced disease it works poorly and more than one dose may be needed. Supportive treatment, including fluids, anti-inflammatory agents, and drugs for pulmonary oedema, is added. Resistance in *T. annulata* has been reported, and a cytochrome b mutation is the proposed basis, so stewardship matters. For *T. parva*, oxytetracycline has been used for prevention alongside a sporozoite immunisation, but it has little curative effect once disease is established.

Histomoniasis (blackhead). *Histomonas meleagridis* affects turkeys most severely and chickens less so. The organism is carried inside eggs of the caecal worm *Heterakis gallinarum*, which protects it in soil. Historically, **nitroimidazoles** (such as dimetridazole and ronidazole) and some arsenicals were used. Many countries have withdrawn or banned nitroimidazoles and arsenical growth or treatment products for food-producing animals because of residue and public health concerns. Hence few or no legal drugs remain in many regions. Whether any such products are permitted in India should be checked in the current notification. Control therefore depends on **prevention**: separating turkeys from chickens, rotating or cleaning ranges, and routine control of Heterakis with an anthelmintic, which breaks the cycle.

Concept cleared

Prophylaxis because damage comes early
In coccidiosis most intestinal damage happens before clinical signs, so anticoccidials work best when given in feed before disease, not after.

Ionophore mechanism and danger
Ionophores carry ions across the parasite membrane and collapse its ion balance. The same effect on a sensitive host such as the horse damages heart and skeletal muscle.

Curative versus prophylactic trypanocides

A trypanocide that persists in tissue protects for weeks but leaves sub-therapeutic levels that select for resistance. A short-lived curative drug does not protect but is less likely to select.

Early buparvaquone

Buparvaquone kills the parasite but cannot rebuild damaged lymphoid tissue, so its benefit falls sharply as disease advances.

Memory aid: Amprolium blocks thiamine

Think AMP-ro-LIUM = 'A Mimic of the vitamin Pro-B1': amprolium copies thiamine and starves the coccidian.

Compare and contrast

Ionophores versus chemical coccidiostats

Feature	Ionophores	Chemical agents
Examples	Monensin, salinomycin, lasalocid, narasin	Amprolium, sulfonamides, diclazuril, toltrazuril, nicarbazin
Mechanism	Carry ions across parasite membrane	Specific steps such as thiamine uptake or folate synthesis
Main use	Continuous feed prophylaxis	Outbreaks or specific prophylaxis by label
Main hazard	Toxic to horses and some species; narrow margin	Species effects such as nicarbazin in layers; resistance
Resistance	Slow to develop but widespread tolerance	Often develops faster

Common trypanocides

Drug	Mainly	Key point
Diminazene	Curative	Also babesicide; sensitive species such as dogs and camels
Isometamidium	Curative and prophylactic	Long persistence, resistance risk
Homidium	Curative	Intercalating agent; injection site reactions
Quinapyramine	Curative or prophylactic by salt	Used in horses, camels, pigs, dogs
Suramin	Curative	Intravenous; poor brain entry

Species notes

Poultry

Feed anticoccidials, rotation or shuttle programmes and live vaccines are central. Observe withdrawal. Nicarbazin is unsuitable for layers. Blackhead control rests on management and worm control.

Cattle and buffalo

Babesiosis, tropical theileriosis and surra all occur. Use babesicides or buparvaquone early, add supportive care, and base control on tick management.

Horses and camels

Horses are highly sensitive to ionophores. Surra occurs in both and quinapyramine and suramin are used. Camels are sensitive to some drugs, so follow labels.

Dogs and cats

Diminazene can cause nervous signs in dogs. Babesia gibsoni and Babesia felis respond poorly to ordinary babesicides. Pups and kittens may have Cystoisospora needing species-appropriate treatment.

Turkeys

Most susceptible to histomoniasis. Keep apart from chickens and control Heterakis.

Clinical pearls

Self-test: 10 questions

1. Why is coccidiosis in poultry controlled mainly by prophylaxis?

By the time signs appear, much epithelial damage has already occurred, so drugs are placed in feed beforehand.

2. Which statement about ionophores is correct?

Ionophores disturb ion gradients; horses are especially sensitive.

3. Amprolium acts by:

Amprolium is a thiamine analogue.

4. A shuttle programme in poultry means:

Two drugs are used within the same flock cycle to slow resistance.

5. Which drug is a nitroimidazole historically used for blackhead but now restricted in many countries?

Nitroimidazoles have been withdrawn in many countries for food animals; check current Indian rules.

6. Which is the main anti-theilerial drug?

Buparvaquone is the principal treatment for Theileria infections.

7. Why is buparvaquone less effective late in disease?

The drug kills parasites but cannot restore destroyed tissue.

8. Which trypanocide gives prolonged prophylaxis but may select resistance?

Persistence in tissues gives protection and leaves sub-therapeutic levels.

9. Which Babesia infections respond poorly to ordinary babesicides?

These species are not readily treated with normal babesicides.

10. Which measure best reduces blackhead risk in turkeys?

Heterakis eggs carry Histomonas, so worm control and separation break the cycle.

Key points to revise

1. Protozoal drugs target pathways absent or different in the host.
2. Coccidiosis is controlled mainly by prophylaxis, since damage precedes signs.
3. Ionophores disturb ion balance; horses are highly sensitive.
4. Amprolium blocks thiamine uptake and is used mainly in outbreaks.
5. Diminazene and imidocarb are the main babesicides; B. gibsoni and B. felis respond poorly.
6. Isometamidium gives prophylaxis but carries a resistance risk.
7. Buparvaquone must be given early in theileriosis; resistance has been reported.
8. Histomoniasis control depends on prevention because few legal drugs remain.

Go deeper on this site

- Ch 17. Antiseptics, disinfectants and farm biosecurity (in this book)
- Ch 15. Ectoparasiticides, insecticides and acaricides (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index

- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Overview of Coccidiosis in Poultry
- Merck Veterinary Manual: Trypanosomiasis in Animals
- Merck Veterinary Manual: Theileriosis in Animals

CHAPTER 17 OF 19

Antiseptics, disinfectants and farm biosecurity

The main classes of antiseptics and disinfectants, why contact time and organic matter decide success, and how teat dips and footbaths fit into farm biosecurity. The chapter also covers choosing a product and its toxicity to animals, people and the environment.

> **After this chapter you can**
>
> - Distinguish antiseptics from disinfectants and explain why the same chemical may be both
> - Describe the main chemical classes with their strengths, limits and toxicity
> - Explain contact time, concentration, organic matter and cleaning before disinfection
> - Explain the purpose and common faults of teat dips and footbaths
> - Apply a simple approach to choosing a disinfectant for a given farm problem

Antiseptic, disinfectant and the idea of biosecurity

An **antiseptic** is applied to living tissue to prevent or suppress infection. A **disinfectant** is a germicide applied to inanimate surfaces such as floors, instruments and milking equipment. The same compound can be either, depending on concentration, contact conditions and number of organisms. For example, a dilute iodine solution can go on skin, but a stronger one is meant for equipment. Both are non-selective, which means they damage microbes and, if misused, host tissue too.

Most act by **denaturing proteins, damaging cell membranes or inhibiting enzymes**. Using more product than needed does not improve results and may

cause toxicity, while too little can leave survivors.

Biosecurity means all procedures that reduce the risk and consequence of infection. Disinfection is only one part. Others include controlling movement of animals, people, vehicles and equipment, quarantine, safe disposal of waste and carcasses, and pest control. A disinfectant works only when it forms part of such a system.

Main classes and what each does well

No single agent is best for everything. Learn each class by its spectrum, its weak points and its toxicity.

- **Alcohols** (ethanol, isopropanol) denature protein. They act quickly, evaporate and are useful for skin and small items. They are poor against bacterial spores and some non-enveloped viruses, and they are inactivated by organic matter. Used alone they leave no residual action.
- **Biguanides: chlorhexidine.** It damages the cell membrane and has good activity against many bacteria, with some residual activity on skin. It is less active against some viruses and spores, and is reduced by organic matter and soap. It can injure the eye and ear, so it should not be put in the middle ear or in the eye.
- **Iodine and iodophors.** Iodine is a broad-spectrum oxidant. Iodophors carry iodine bound to a carrier, so they irritate less. They are useful in surgery preparation and teat dips. They are inactivated by organic matter and can stain.
- **Chlorine compounds** (hypochlorite). These are cheap and effective against many bacteria and viruses. They are strongly inactivated by organic matter and corrode metals. Chlorine gas can be released if bleach is mixed with acids, and a toxic gas can also form if mixed with ammonia.
- **Quaternary ammonium compounds** (QACs). Surfactants that disrupt membranes. They are good cleaners and low in odour, but are weaker against non-enveloped viruses and some Gram-negative bacteria, and are inactivated by soap residues and hard water.
- **Phenols and cresols.** Active in the presence of some organic matter. They are toxic to cats and also to pigs and young animals if misused, and can be absorbed through skin. Avoid in cat housing.

- **Alkalis and acids** (sodium hydroxide, lime, washing soda, citric acid). Used for specific viruses, for example in foot and mouth disease control, and for housing. They are caustic and need protective equipment.

Contact time, concentration and organic matter

Three factors decide whether a disinfectant works: **concentration, contact time and cleanliness of the surface**. Contact time is the period the surface must stay wet with the product at the stated dilution. A product sprayed and wiped off in seconds has not been given the chance to act. The label states the time for each target organism, and the value for spores or non-enveloped viruses is much longer than for ordinary bacteria.

Organic matter (manure, blood, milk, pus, soil) is the commonest cause of failure. It physically shields microbes and chemically reacts with the active agent. Chlorine, iodine and QACs are especially affected. Therefore the sequence is: remove gross dirt, wash with detergent, rinse, then disinfect, then allow to dry. A disinfectant is not a substitute for cleaning.

Other factors are temperature (warmer is generally faster, within limits), pH, water hardness, and mixing of incompatible products. **Never mix disinfectants**. Mixing can neutralise them or produce toxic gas.

Teat dips

Teat dipping is a mastitis control step. Contagious pathogens such as *Staphylococcus aureus* and *Streptococcus agalactiae* spread at milking, and the teat canal stays open for a period after milking. A **post-milking dip** kills organisms on the teat skin and reduces new infections. A **pre-milking dip** targets environmental bacteria and must be wiped off before the cluster is attached, giving a suitable contact time, to avoid residues in milk.

Common active ingredients include iodophors, chlorhexidine, chlorine-releasing products and organic acids, often with emollients to protect skin. Points to remember:

- Cover the whole teat, not just the tip. Dipping or spraying must wet all the skin.
- Use a fresh dip. Dip cups and sprayers get contaminated, and organic matter reduces activity. Do not return used dip to the stock bottle.

- Observe contact time and wipe pre-dip off thoroughly.
- Product choice must follow the label, and the dip should be a product licensed for use on teats.

Teat dips do not cure existing infection. They reduce new infection. They are part of a programme that includes milking hygiene, machine maintenance, dry cow therapy as advised by a veterinarian, and culling of chronically infected animals.

Footbaths

Footbaths are used to control infectious foot lesions in cattle and sheep, such as digital dermatitis, and also as a biosecurity step at the entrance to a unit. They are only useful if used properly. Common agents are copper sulfate, formalin, zinc sulfate and peracetic acid-based products.

Common faults: the bath is too short, so the animal's feet are not fully submerged for adequate time; the bath is overloaded with manure so that the active ingredient is inactivated; the solution is not renewed after the set number of animals; and the animals walk in with dirty feet. Boots must be scrubbed clean first and then dipped.

A footbath is a **supporting measure**. It cannot fix poor floors, wet standing, poor hoof trimming or untreated lame animals. The Merck Veterinary Manual notes that foot baths may be considered in an outbreak as part of tackling indirect transmission.

Safety and environment. Formalin is irritant and hazardous to people. Copper and zinc can build up in slurry and soil and harm crops, microbes and sheep (sheep are sensitive to copper). Spent footbath solution should be disposed of according to local environmental guidance, not poured into watercourses.

Choosing a disinfectant and toxicity

An ideal disinfectant is broad-spectrum, fast, stable, active despite some organic matter, not corrosive, not toxic and affordable. No product meets all these, so a choice is made by asking four questions.

1. **What is the target?** Bacteria, enveloped virus, non-enveloped virus, spores, oocysts or fungi. Oocysts of coccidia resist many common disinfectants, and heat or specific products are needed.

2. **What is the surface and how dirty?** Porous concrete and wood hold organic matter. Metal can corrode.
3. **Who and what is exposed?** Animals present, staff, milk or food contact, and drainage into the environment.
4. **Is it licensed and legal?** Use products licensed for animal use and follow local regulations. For notifiable disease outbreaks, officials may specify the disinfectant and its concentration. Check the current guidance rather than relying on memory.

Toxicity must be considered each time. Phenols are dangerous to cats. Iodine can cause thyroid effects if absorbed in quantity, particularly in neonates. Chlorhexidine harms the middle ear and eye. QACs and aldehydes irritate skin and airways. Alkalis burn. Fumes from chlorine mixtures injure the lungs of animals and staff.

Concept cleared

Clean first, then disinfect
Organic matter shields microbes and inactivates chlorine, iodine and QACs, so washing with detergent comes before disinfection.

Contact time
A disinfectant needs time wet on the surface at the right dilution. Spraying and wiping immediately gives little kill.

More is not better
Over-strong solutions add toxicity without extra kill, and under-strength solutions leave tolerant survivors.

Teat dips prevent, not cure
A teat dip reduces new intramammary infection after milking. It does not treat an established infection.

Memory aid: CCC before disinfecting

Clean, Contact time, Concentration: remove dirt first, give the product time, and mix at the label strength.

Compare and contrast

Main disinfectant classes

Class	Strength	Main limit or hazard
Alcohols	Fast skin and small item action	No spore kill, evaporate, no residual
Chlorhexidine	Good bacterial action, residual on skin	Ear and eye injury; reduced by organic matter
Iodophors	Broad, used for surgery and teats	Inactivated by organic matter; stains; absorption
Hypochlorite	Cheap, broad	Inactivated by organic matter; corrosive; toxic gas with acid or ammonia
Peroxygens	Broad, includes many viruses	Corrosive and irritant at strength
QACs	Good cleaning action	Weak on non-enveloped viruses; inactivated by soap
Phenols	Tolerate some organic matter	Toxic to cats and young animals

Antiseptic versus disinfectant

Feature	Antiseptic	Disinfectant
Applied to	Living tissue	Inanimate surfaces
Tolerance needed	Must not damage tissue	May be harsher
Examples	Chlorhexidine, dilute iodophor	Hypochlorite, peroxygens, QACs
Same chemical?	Yes, at lower concentration	Yes, at higher concentration

Species notes

Dairy cattle

Poultry and pigs

Teat dips after milking, clean udders before milking, and footbaths for digital dermatitis. Mind residues in milk and copper in slurry.

All-in all-out, clean-out and drying before disinfection. Oocysts need special products or heat. Keep a footbath or boot change at each house.

Cats
Very sensitive to phenols and cresols. Avoid these in cat housing, clinics and on surfaces cats lick.

Sheep
Sensitive to copper, so take care with copper sulfate footbaths and spent solution.

Dogs and small animal clinics
Chlorhexidine and alcohol for skin, and suitable surface products for wards. Keep chlorhexidine out of the ear and eye.

Clinical pearls

Self-test: 10 questions

1. An antiseptic is applied to:

Antiseptics are used on body tissues; disinfectants are for surfaces.

2. Which is the commonest cause of disinfectant failure?

Organic matter shields microbes and inactivates many agents.

3. Which class is particularly dangerous to cats?

Cats are sensitive to phenols and cresols.

4. What should never be done with household bleach?

Mixing releases toxic gases.

5. Alcohols are poor against:

Alcohols do not reliably kill spores.

6. A post-milking teat dip mainly:

It lowers the spread of organisms at and after milking.

7. A common reason footbaths fail is:

Manure inactivates the active ingredient.

8. Contact time refers to:

The disinfectant needs time wet on the surface at the correct dilution.

9. Which is true of QACs?

Anionic soap residues reduce QAC activity, and non-enveloped viruses are less susceptible.

10. Which is a concern with copper sulfate footbaths?

Copper accumulates in the environment and sheep are sensitive to it.

Key points to revise

1. Antiseptics are for tissues and disinfectants for surfaces; many chemicals serve as both.
2. Most agents denature protein, damage membranes or inhibit enzymes.
3. Alcohols are fast but do not kill spores.
4. Chlorine, iodine and QACs are inactivated by organic matter.
5. Contact time, concentration and prior cleaning determine success.
6. Teat dips lower new infections but do not cure existing ones.
7. Footbaths need renewal, cleaning of boots first and proper disposal of spent solution.
8. Choose by target, surface, exposure and legal status, and check toxicity.

Go deeper on this site

- Ch 18. Anticancer drugs (in this book)
- Ch 16. Antiprotozoal drugs (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Overview of Antiseptics and Disinfectants
- Merck Veterinary Manual: Antiseptics and Disinfectants
- Merck Veterinary Manual: Principles of Biosecurity

CHAPTER 18 OF 19

Anticancer drugs

Why conventional cytotoxic drugs kill fast-dividing cells, how the main drug classes work, and why bone marrow, gut and other tissues suffer. Also covers resistance, combination protocols, species-specific toxicities and the safe handling of hazardous drugs.

> **After this chapter you can**

- Explain the cytotoxic principle and why normal rapidly dividing tissues are also injured
- Distinguish cell-cycle-specific from cell-cycle-nonspecific agents and link each to a drug class
- Describe the mechanism of the main classes of anticancer agents with one example each
- Predict the common adverse effects and the species-specific toxicities to remember
- State the principles of safe handling and disposal of cytotoxic drugs

The cytotoxic principle

Conventional anticancer drugs are **cytotoxic**. They damage DNA, block DNA or RNA synthesis, or disturb the machinery of cell division. Cells that divide often are hit hardest. Tumour cells divide often, so they are injured, but so are normal tissues that renew quickly: bone marrow, intestinal lining, hair follicles and germ cells.

This is the root of the narrow therapeutic index. The drug has no real way to tell a tumour cell from a healthy dividing cell. The more drug given, the more tumour cells are killed, so treatment usually aims for the highest dose the patient can tolerate. The limit is set by damage to normal tissue, mostly the marrow.

Chemotherapy may be given before surgery or radiation (neoadjuvant), after it (adjuvant), or alone. The aim ranges from complete remission in sensitive tumours such as lymphoma, to palliation and better quality of life in others. In veterinary practice the aim is usually a good quality of life, not cure at any cost.

Cell cycle and drug classes

A cell passes through G1, S (DNA synthesis), G2 and M (mitosis). Some cells rest in G0 and are largely spared by drugs that need active division.

- **Cell-cycle-nonspecific agents** act in any phase, including resting cells. Kill increases with concentration. Alkylating agents are the main example.
- **Cell-cycle-specific agents** act in one phase. Antimetabolites work mostly in S phase. Vinca alkaloids and taxanes work in M phase. These drugs work best on tumours with many dividing cells and are often given repeatedly.

This idea explains why protocols give drugs in cycles. Each cycle kills a fixed fraction of cells, not a fixed number. A drug that cycle-nonspecifically reduces the tumour may push surviving cells into division, where a phase-specific drug can then reach them. Rest periods between cycles let the marrow and gut recover.

Common confusion: students think chemotherapy kills a fixed number of cells per dose. It kills a fraction, so repeated cycles are needed, and a few surviving resistant cells can regrow the tumour.

Main agents and their mechanisms

Learn each class by its target.

- **Alkylating agents** (cyclophosphamide, chlorambucil, lomustine) add alkyl groups to DNA and cause cross-links and strand breaks. **Platinum compounds** (cisplatin, carboplatin) act in a similar way by cross-linking DNA.
- **Antimetabolites** (methotrexate, cytarabine, 5-fluorouracil, gemcitabine) resemble normal building blocks. Methotrexate blocks dihydrofolate reductase and so reduces the thymidine and purines needed for DNA. Cytarabine is a false nucleoside that blocks DNA synthesis.
- **Anticancer antibiotics** (doxorubicin, mitoxantrone, bleomycin) bind or break DNA. Doxorubicin intercalates into DNA and inhibits topoisomerase II.
- **Mitotic inhibitors**. Vinca alkaloids (vincristine, vinblastine) block microtubule assembly, so the spindle cannot form. Taxanes (paclitaxel) stabilise microtubules so they cannot disassemble. Either way mitosis fails.
- **Hormonal and lympholytic agents**. Glucocorticoids such as prednisolone kill lymphoid cells and are part of lymphoma protocols.
- **Miscellaneous**. L-asparaginase removes asparagine, which some lymphoid tumour cells cannot make for themselves. Hydroxyurea blocks ribonucleotide reductase.
- **Targeted agents** act on specific molecular markers or abnormal signalling pathways, for example tyrosine kinase inhibitors used in some canine tumours. They are generally more selective, though not free of toxicity.

Combination protocols and resistance

Tumours are seldom treated with one drug. Combination protocols use drugs with **different mechanisms and different dose-limiting toxicities**. This increases tumour kill without adding up the same toxicity, and it lowers the chance that one resistant clone survives.

Resistance arises because tumours are genetically unstable. Some cells carry changes that allow survival, and these are selected by treatment. Common mechanisms:

- Increased efflux of drug by P-glycoprotein (the MDR1 or ABCB1 pump), which lowers intracellular drug.
- Reduced drug uptake or reduced activation of a prodrug.
- Increased DNA repair.
- Altered drug target, for example more dihydrofolate reductase.
- Cells resting in G0 that escape phase-specific drugs.

Resistance to one drug can give **cross-resistance** to others that are pumped out by the same transporter. Large tumours have more cells and so more chance of a resistant clone, which is one reason early treatment of small tumour burden works better.

Adverse effects and species-specific toxicities

Predict toxicity from tissue turnover.

- **Myelosuppression** is the commonest dose-limiting effect. Neutropenia typically appears about a week after treatment and is the main danger because of sepsis. Blood counts are therefore checked around the expected nadir, and a febrile neutropenic patient is an emergency.
- **Gastrointestinal**: nausea, vomiting, diarrhoea, mucosal damage. Antiemetics are used for prevention or treatment.
- **Sterile haemorrhagic cystitis** from cyclophosphamide, because its metabolite acrolein irritates the bladder. It is reduced by encouraging urination and by protective agents.
- **Cardiotoxicity** from doxorubicin is cumulative and dose-related in dogs, so total exposure is tracked. In cats the same drug is more of a kidney concern.

- **Extravasation** of vesicant drugs such as doxorubicin and vincristine causes severe tissue necrosis, so intravenous access must be secure.
- **Others**: hair loss (especially in breeds with continuously growing coat), reduced fertility, and harm to the foetus.

Remember the species traps: **cisplatin is contraindicated in cats**, and **5-fluorouracil is dangerous for cats** because of neurotoxicity. Collies and related breeds with the MDR1 mutation may show more toxicity from drugs that are P-glycoprotein substrates, such as vincristine and doxorubicin. Dosing is often by body surface area, though very small animals may need adjusting; follow a current protocol and specialist advice.

Safe handling and disposal

Cytotoxic drugs can harm the people who handle them as well as the patient. Many are carcinogenic, mutagenic or toxic to reproduction. Exposure occurs through skin contact, inhalation of aerosols or dust, accidental needle injury, and contact with patient urine, faeces or vomit, since drug and metabolites are excreted for a period after dosing.

Basic principles, in line with occupational health guidance such as that from NIOSH:

- Prepare drugs in a designated area, ideally in a ventilated safety cabinet, and avoid creating aerosols.
- Wear appropriate protective equipment: suitable chemotherapy-rated gloves (often double), a closed gown and eye protection. Do not use tablets in a way that crushes or splits them in open air.
- Use closed or luer-lock systems to reduce spills and leaks.
- Label drugs and waste clearly. Place used items in separate, sealed cytotoxic waste containers for proper disposal, not ordinary rubbish or sinks.
- Have a spill kit and know the spill procedure.
- Pregnant, breastfeeding or trying-to-conceive staff should avoid handling these drugs.
- Advise owners to wear gloves when handling the patient's excreta for the period advised by the clinician and to wash hands afterwards.

For disposal rules, biomedical waste requirements in India, and any limits on use of particular drugs in animals, check the current notification and institutional policy.

Concept cleared

Fractional cell kill

Each cycle of chemotherapy kills a fraction of tumour cells, not a fixed number. Repeated cycles and combination drugs are needed, and any surviving resistant cells can regrow.

Narrow therapeutic index

Cytotoxic drugs cannot distinguish tumour from healthy dividing cells. Doses are pushed to the edge of marrow and gut tolerance, so toxicity is expected and must be monitored.

Cell-cycle specificity

Phase-specific drugs (antimetabolites in S, vinca alkaloids in M) need dividing cells. Nonspecific drugs (alkylating agents) also act on resting cells. This shapes scheduling and drug sequencing.

Multidrug resistance

Efflux pumps such as P-glycoprotein can remove several unrelated drugs from tumour cells, giving cross-resistance. The same pump is involved in the canine MDR1 mutation.

Memory aid: Mitotic poisons

VINCA = Vincristine Inhibits Nascent Cytoskeleton Assembly (stops spindle building), while taxanes do the opposite and freeze microtubules. Either way: M phase stops.

Compare and contrast

Major classes of cytotoxic drugs

Class	Example	Main mechanism	Cell-cycle effect
Alkylating agents	Cyclophosphamide, lomustine	Cross-link and break DNA	Mostly nonspecific
Platinum compounds	Carboplatin, cisplatin	DNA cross-links	Mostly nonspecific
Antimetabolites	Methotrexate, cytarabine	Block DNA synthesis	S phase
Anticancer antibiotics	Doxorubicin	Intercalate DNA, inhibit topoisomerase II	Mostly nonspecific
Vinca alkaloids	Vincristine	Prevent microtubule assembly	M phase
Taxanes	Paclitaxel	Stabilise microtubules	M phase

Toxicity to remember by drug

Drug	Characteristic toxicity	Note
Cyclophosphamide	Sterile haemorrhagic cystitis	Caused by acrolein
Doxorubicin	Cardiotoxicity in dogs, extravasation injury	Cumulative exposure tracked
Vincristine	Extravasation, neuropathy, marrow effects	Vesicant
Cisplatin	Kidney injury, vomiting	Contraindicated in cats
5-Fluorouracil	Neurotoxicity	Dangerous in cats

Species notes

Dog

Lymphoma is the most common tumour treated with multi-drug protocols. Doxorubicin cardiotoxicity is cumulative. MDR1-mutant breeds

Cat

Cisplatin and 5-fluorouracil are unsafe. Doxorubicin tends to affect the kidney. Cats rarely lose body hair but may lose whiskers.

may have more toxicity from some drugs.

Horse
Cytotoxic drugs are used rarely. Local treatments such as intralesional cisplatin or carboplatin implants for skin tumours are an example.

Cattle and food animals
Systemic chemotherapy is rarely used because of cost and the problem of drug residues in food. Check current regulations before any use in food-producing animals.

Small pets and owners
Excreta of treated pets contain drug for some days, so owners need clear handling advice.

Clinical pearls

Self-test: 10 questions

1. Why do conventional anticancer drugs commonly cause marrow suppression and vomiting?

Marrow and gut epithelium renew quickly, so they are damaged along with tumour cells.

2. Which statement about cell-cycle-nonspecific drugs is correct?

Alkylating agents are the typical example.

3. Which drug class mainly acts in S phase by mimicking normal building blocks?

Antimetabolites such as methotrexate and cytarabine interfere with DNA synthesis.

4. Vincristine acts by:

Without microtubules no mitotic spindle forms, so M phase is blocked.

5. Sterile haemorrhagic cystitis is characteristic of:

Its metabolite acrolein irritates the bladder wall.

6. Which drug is contraindicated in cats?

Cisplatin is unsafe in cats, and 5-fluorouracil is also dangerous for them.

7. A common mechanism of multidrug resistance in tumour cells is:

Efflux pumps lower intracellular drug and can cause cross-resistance.

8. Why are combination protocols used?

Drugs with different targets and different dose-limiting effects are combined.

9. Which is the safest practice when handling cytotoxic tablets or injections?

Reduce skin, aerosol and needle exposure, and dispose of waste properly.

10. Doxorubicin in dogs is particularly associated with:

Cumulative dose is tracked to limit cardiac damage.

Key points to revise

1. Cytotoxic drugs kill rapidly dividing cells, normal and tumour.

2. The therapeutic index is narrow and the marrow is usually dose limiting.
3. Cells in G0 are relatively resistant to phase-specific drugs.
4. Alkylating agents and platinum compounds damage DNA by cross-linking.
5. Antimetabolites act in S phase; vinca alkaloids and taxanes in M phase.
6. Combination protocols use drugs with different mechanisms and different toxicities.
7. P-glycoprotein efflux is a major route of multidrug resistance.
8. Cytotoxic drugs are hazardous to handlers and need strict handling and waste rules.

Go deeper on this site

- Ch 19. Immunopharmacology (in this book)
- Ch 17. Antiseptics, disinfectants and farm biosecurity (in this book)
- Veterinary drugs list: classes, uses and cautions
- Veterinary Drug Index
- Veterinary Drug Concepts Clearly Explained

Sources

- Merck Veterinary Manual: Overview of Antineoplastic Agents
- NIOSH: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings
- Merck Veterinary Manual: Cancer Treatment in Animals

CHAPTER 19 OF 19

Immunopharmacology

How drugs and biological products are used to build, suppress, boost or borrow immunity: vaccine types, immunosuppressants, immunostimulants, antisera and antitoxins, and monoclonal antibodies. The focus is on mechanism, why products succeed or fail, and the safety and residue logic that follows.

After this chapter you can

- Distinguish active from passive immunity and give a product example of each

- Compare killed, modified live, subunit, toxoid and recombinant vaccines with their advantages and risks
- Explain how common immunosuppressants work and what their main risks are
- Describe the logic of antisera, antitoxins and immunostimulants
- Explain how monoclonal antibodies act and why they differ from small-molecule drugs

Active and passive immunity

Immunopharmacology deals with products that change the immune system for benefit. The first idea to fix is the difference between two kinds of protection.

Active immunity means the animal's own immune system makes antibodies and memory cells after infection or vaccination. It takes days to develop but is long-lasting and rapidly recalled on re-exposure. **Passive immunity** means ready-made antibodies are supplied from outside, such as colostrum from the dam or antiserum given by injection. Protection is immediate but temporary, because the antibodies are gradually broken down and no memory is created.

A vaccine therefore builds protection for the future, while an antiserum or antitoxin treats or prevents an immediate threat. Mixing up these two is a common examination error.

Vaccines: types and what they mean

A vaccine presents antigen without causing the disease. How the antigen is prepared decides its strength, safety and need for boosters.

- **Killed (inactivated)** vaccines use organisms killed by chemicals. They cannot revert to virulence and are stable, but they usually give a weaker, antibody-dominated response and need adjuvants and repeated doses.
- **Modified live (attenuated)** vaccines use weakened organisms that multiply in the host. They usually give a stronger and longer response, including cell-mediated immunity, but can in principle revert to virulence, can be shed to other animals, are damaged by heat and poor cold chain, and may be unsafe in pregnant or immunosuppressed animals.

- **Subunit** vaccines contain purified protective antigens, avoiding unneeded or toxic parts.
- **Toxoid** vaccines are inactivated toxins, for example tetanus toxoid. They protect by producing antibodies against the toxin.
- **Recombinant and vector vaccines** use cloned antigens or insert protective genes into a harmless carrier. Gene-deleted and vectored vaccines can allow infected animals to be told apart from vaccinated ones (DIVA).

Adjuvants boost the response by increasing local inflammation. They are mostly needed for killed and purified vaccines, and they can cause local reactions or hypersensitivity.

Why vaccines fail or cause problems

Vaccine failure is usually not the product alone. Think through the causes:

- **Maternal antibody interference.** Antibodies from colostrum neutralise vaccine antigen in young animals, especially with live vaccines, so early doses may not take. This is why young animals need repeated doses until maternal antibody has faded.
- **Cold chain and handling errors.** Heat, light or freezing can destroy live vaccines.
- **Immunosuppression, stress, malnutrition and heavy parasite burden** weaken the response.
- **Wrong antigen.** A vaccine works only against the strains and pathogens it contains. A disease with several causes, such as bovine respiratory disease, is not controlled by one organism's vaccine.
- **Giving a modified live vaccine and antiserum together**, since the antibody will neutralise the vaccine organism.

Adverse effects include local swelling, fever, allergic reactions, and rarely injection-site problems. For some diseases, such as feline infectious peritonitis and equine infectious anaemia, antibody may contribute to disease, so a vaccine cannot be assumed to help. Vaccine use should follow the current national schedule and manufacturer instructions; check the current notification for regulations on licensed products in India.

Immunosuppressants

Immunosuppressants are used in immune-mediated disease, such as immune-mediated haemolytic anaemia and thrombocytopenia, atopic skin disease, and to prevent graft rejection. They reduce immune activity in a broad, not antigen-specific, way.

- **Glucocorticoids** (prednisolone, dexamethasone) bind nuclear receptors, reduce cytokine production, kill lymphocytes and reduce antibody-coated cell clearance. They are the first-line choice but have many side effects with long use.
- **Azathioprine** is a purine antimetabolite that lowers lymphocyte proliferation. It is used with steroids to spare dose. Cats are highly sensitive to its marrow toxicity and it is generally avoided in them.
- **Cyclosporine** inhibits calcineurin and so reduces activation of T cells and IL-2 production. It is used in atopic dermatitis and some immune-mediated conditions.
- **Cytotoxic drugs** such as cyclophosphamide or mycophenolate, used for severe disease in some cases.

The main risks are infection, delayed wound healing, marrow suppression for some drugs, and drug-specific toxicity. A response is slow to appear for the non-steroid drugs, so patience and monitoring matter. Never stop long-term steroids suddenly, because the adrenal axis is suppressed.

Immunostimulants, antisera and antitoxins

Immunostimulants aim to raise immune activity, for example by acting on macrophages or inducing cytokines. Examples include bacterial-derived products, levamisole in some uses, and interferons. Evidence for many products used in practice is limited, so claims should be treated with caution. Vitamin and mineral deficiencies and parasitism, if present, should be corrected first.

Antisera and antitoxins are passive immunity products. They contain antibodies, often from hyperimmunised animals (frequently horses), against a microbe or toxin.

- **Antitoxin** neutralises a toxin that is free in the body, for example tetanus antitoxin and snake antivenom. It must be given early, because it cannot reverse toxin already bound to tissue.

- **Antiserum** provides antibody against an organism, used to give quick cover in a high-risk situation.

Because these products are foreign protein, they can cause **serum sickness or anaphylaxis**, especially on repeat use, so facilities for emergency treatment should be ready. Protection lasts weeks at most. Animals given tetanus antitoxin still need toxoid for lasting immunity, given at a separate site.

Monoclonal antibodies

A **monoclonal antibody** (mAb) is a single, identical antibody engineered to bind one target very precisely. In veterinary medicine they are now used for specific signals, not for a whole organism.

Examples:

- **Lokivetmab** is a caninised antibody that neutralises IL-31, a cytokine linked to itch in canine atopic dermatitis.
- **Bedinvetmab** (dogs) and **frunevetmab** (cats) bind nerve growth factor, which blocks an osteoarthritis pain pathway.

Concepts to understand:

- **Speciation.** The antibody is caninised or felinised so the patient's body does not see it as foreign. A well-matched antibody is less likely to trigger anti-drug antibodies, though they can still occur and may reduce effect.
- **No liver or kidney metabolism.** Antibodies are broken down as proteins, so drug interactions are fewer, and the half-life is long, allowing injections at long intervals.
- **Target biology predicts side effects.** Blocking a normal signal may have consequences that match what that signal does.
- **Cost and specificity.** They are targeted and expensive, and do not replace general diagnosis and management.

The suffix **-mab** identifies monoclonal antibodies, and a species stem such as *-vet-* marks them for veterinary use. Check the current regulatory status of these products for India.

Concept cleared

Active versus passive immunity

Active immunity is made by the host and has memory but is slow. Passive immunity is borrowed antibody that works at once but fades and leaves no memory.

Live versus killed vaccine trade-off

Live vaccines give stronger and longer immunity but carry reversion, shedding and cold-chain risks. Killed vaccines are safer and stable but weaker and need adjuvant and boosters.

Maternal antibody interference

Colostral antibody protects the newborn but also neutralises vaccine antigen, so early vaccination may fail and repeated doses are scheduled.

Specificity of monoclonal antibodies

A mAb blocks one chosen molecule. This gives precision and few metabolic interactions, but effects follow the target's biology and anti-drug antibodies can develop.

Memory aid: Passive products

PASSIVE = Prompt, Antibody supplied, Short-lived, Substitute for memory, Immediate cover, Very temporary, Ends soon. Active products are slow but remembered.

Compare and contrast

Vaccine types

Type	Strength of response	Main advantage	Main concern
Killed	Weaker, antibody	Cannot revert, stable	Needs adjuvant and boosters
Modified live	Stronger, includes cell-mediated	Long immunity	Reversion, shedding, cold chain, pregnancy
Subunit or toxoid	Antibody to selected antigen	No unneeded components	Needs adjuvant, boosters
Recombinant or vectored	Varies by design	Safe, can allow DIVA	Product specific

Active versus passive products

Feature	Vaccine or toxoid	Antiserum or antitoxin
Type of immunity	Active	Passive
Onset	Days to weeks	Immediate
Duration	Long, with memory	Short, no memory
Typical use	Prevention	Emergency treatment or short-term cover
Key risk	Local or allergic reaction, failure	Serum sickness or anaphylaxis

Species notes

Dog and cat

Core vaccines follow a schedule that accounts for maternal antibody. Lokivetmab and bedinvetmab are used in dogs, frunevetmab in cats. Cats are especially sensitive to azathioprine.

Cattle and buffalo

Mass vaccination against diseases like foot-and-mouth disease and haemorrhagic septicaemia depends on cold chain and correct schedules. Check the current national programme.

Horse

Poultry

Tetanus toxoid is routine, and tetanus antitoxin gives temporary cover after a wound in an unvaccinated horse. Horse-derived antisera are a major source of antitoxins.

Flock vaccination uses live and killed products by different routes. Maternal antibody in chicks can interfere with early vaccination.

Sheep and goat

Clostridial toxoid vaccines are widely used. Check the current manufacturer schedule for dams, because colostral transfer protects lambs and kids.

Clinical pearls

Self-test: 10 questions

1. Which is an example of passive immunity?

Colostrum supplies ready-made antibody. The others produce active immunity.

2. A main disadvantage of modified live vaccines is:

Live organisms multiply and may revert or spread to other animals.

3. Tetanus toxoid is an example of:

It is a formalin-inactivated toxin that produces antitoxin antibodies.

4. Why might a puppy fail to respond to an early live vaccine?

Maternal antibodies bind vaccine antigen, so repeated doses are scheduled.

5. Cyclosporine suppresses immunity mainly by:

Calcineurin inhibition reduces IL-2 production and T-cell activation.

6. Which drug is particularly risky for marrow suppression in cats?

Cats are deficient in the enzyme that detoxifies it, so azathioprine is generally avoided.

7. An antitoxin is most useful when:

It neutralises circulating toxin and cannot reverse bound toxin.

8. A major risk of repeated horse-derived antiserum in other species is:

Foreign protein can trigger hypersensitivity, especially on repeat exposure.

9. Lokivetmab acts by:

It is a caninised antibody that binds the itch-related cytokine IL-31.

10. Why do monoclonal antibodies have few metabolic drug interactions?

Antibodies are catabolised to amino acids, so CYP-based interactions are not a concern.

Key points to revise

1. Active immunity is host-made and has memory; passive immunity is supplied antibody and is temporary.
2. Modified live vaccines are strong but carry reversion, shedding and cold-chain risks.
3. Killed and subunit vaccines are safer but usually need adjuvant and boosters.

4. Maternal antibody can block vaccine response in the young.
5. Glucocorticoids, azathioprine and cyclosporine suppress immunity by different mechanisms.
6. Cats are sensitive to azathioprine marrow toxicity.
7. Antisera and antitoxins can cause serum sickness or anaphylaxis.
8. Monoclonal antibodies bind one target, are speciated to lower immunogenicity, and have long half-lives.

Go deeper on this site

- Ch 18. Anticancer drugs (in this book)
- Ch 17. Antiseptics, disinfectants and farm biosecurity (in this book)
- Veterinary drugs list: classes, uses and cautions
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Sources

- Merck Veterinary Manual: Types of Vaccines for Animals
- Merck Veterinary Manual: Active Immunity in Animals
- Current Review of Monoclonal Antibody Therapeutics in Small Animal Medicine (PMC)

How to use Book 3: a short discussion

Chemotherapy means treating disease with drugs that harm the invader while sparing the host. In veterinary practice that covers bacteria, fungi, viruses, worms, ticks, protozoa and cancer cells, and it also covers the quieter work of disinfection and immune modulation. This book gathers those topics into nineteen chapters. Unlike the systemic drugs in Book 2, these medicines are chosen by the organism more than by the organ, so the questions change: what is the target, how will it become resistant, and what will remain in milk, meat or eggs?

Start with the principles

Chapter 1 explains how to choose an antibacterial drug: spectrum, killing versus inhibiting, how concentration and time shape the effect, and why a culture and sensitivity test is worth the wait. Chapter 9 explains resistance and stewardship, the habits that keep drugs working. Read these two first. Every class chapter in between is easier once you can see why a drug is chosen, not only what it does.

Class by class

Chapters 2 to 8 walk through the antibacterial classes in a consistent pattern: how the drug works, where it reaches, what it is good for, what can go wrong, and how bacteria escape it. The same pattern is used for antifungal, antiviral and antiparasitic drugs. Comparison tables set related drugs side by side, which is how most examination questions are framed.

Food safety is part of pharmacology

In food animals a drug is not finished when the animal recovers. Residues of antimicrobials can pass into milk, meat, eggs and honey, and they contribute to resistance in the wider community. Chapters 10 and 11 explain withdrawal periods, maximum residue limits and mastitis therapy in plain terms. Because Indian rules and limits are revised from time to time, the book points you to the current notification rather than printing numbers that may be out of date.

No dose tables, and why

As in the earlier books, there are no dose tables. A dose depends on the product, the species, the route and the country, and it should come from the label or a current formulary. What the book gives you is the reasoning that makes a dose sensible, so that you can recognise a poor choice even when a number looks plausible.

Making the most of the self-tests

Each chapter ends with ten questions and an explanation for every answer. Attempt them before reading the Revise points, and repeat a chapter after a week. Use the search box to find a drug or a term and then read the surrounding chapter so the fact stays connected to its mechanism.

Parasites, cancer and the immune system

The later chapters widen the idea of chemotherapy. Anthelmintics, ectoparasiticides and antiprotozoal drugs are the daily tools of livestock practice in India, where worms, ticks and blood parasites cause steady losses. The same resistance logic applies to them as to antibiotics: under-dosing, treating every animal at every visit and rotating drugs without thought all push resistant parasites to the front. The chapter on anticancer drugs explains how cytotoxic agents work, why they harm fast-dividing healthy tissues, and how staff are protected when handling them. The final chapter on immunopharmacology links vaccines, antisera and immunosuppressive drugs, showing how drugs can also be used to switch an immune response on or off.

A note on evidence

Therapy keeps changing as new resistance patterns appear and new products are approved. Treat this book as the stable framework, and check current guidelines, product labels and local regulations before acting on any specific detail.

Continue with the related guides on this site, including the veterinary drugs list and the Drug Index, to link each class to real products and cases. This material is written for education and does not replace the judgement of a registered veterinarian.